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AIR FORCE HEALTH STUDY
SUMMARY OF FINDINGS IN THE RANCH HAND GROUP

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This report is a compilation and discussion of the findings from AFHS research related to the mortality, reproductive outcomes, and morbidity components of the AFHS. Subsequent to the protocol, published in 1982, the baseline physical examination was conducted in 1982, and follow-up examinations were performed in 1985, 1987, 1992, 1997, and 2002. Findings from technical reports such as the physical examinations, letters to the editor and journal articles published as of 30 September 2006 are described in the appropriate chapters of the report.

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13 January 1982 to 30 September 2006

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1. INTRODUCTION

This chapter describes the purpose and background of the Air Force Health Study (AFHS) and provides an overview of the study design and format of this report.

1.1. PURPOSE OF THE REPORT

This report is a compilation and discussion of the findings from AFHS research related to the mortality, reproductive outcomes, and morbidity components of the AFHS. Subsequent to the protocol, published in 1982 (1), baseline physical examinations were conducted in 1982, and follow-up examinations were performed in 1985, 1987, 1992, 1997, and 2002. Findings from technical reports such as the physical examinations (2-8), letters to the editor and journal articles published as of 30 September 2006 are described in the appropriate chapters.

The objective of the AFHS was to determine whether long-term health effects among Ranch Hand veterans existed that could be attributed to occupational exposure to herbicides, with specific emphasis on Agent Orange, a one-to-one mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In this report, the use of the term "dioxin" refers to TCDD. Starting with the 1987 physical examination, the AFHS investigators used dioxin levels as a surrogate for exposure, as derived from the early peer review groups, review of the literature, and the Ranch Hand Advisory Committee. Although there are approximately 75 different congeners of dioxin, dioxin is believed to be the most toxic and was a contaminant of 2,4,5-T.

The findings in the articles may differ from the physical examination reports because they may (a) combine data from two or more physical examinations, (b) use different methods of analysis, (c) focus on specific health endpoints, or (d) include different risk factors. The results in the journal articles are often consistent, but sometimes lead to conclusions that differ from the seven physical examination reports. For example, published articles on diabetes in Ranch Hand veterans revealed an association with dioxin exposure consistent with the examination report. Published articles on cancer, however, revealed associations not examined in the examination reports.

1.2. BACKGROUND

In January 1962, Operation Ranch Hand, the designation for the aerial spraying of herbicides, began for the purpose of defoliation and crop destruction in support of tactical military operations in the Republic of Vietnam (RVN) (9). The herbicides sprayed were code-named Herbicide Green, Herbicide Pink, Herbicide Purple, Herbicide Orange, Herbicide White, and Herbicide Blue. 2,4,5-T was an active ingredient in Herbicides Green, Pink, Purple, and Orange, and dioxin was produced as an inadvertent contaminant of 2,4,5-T during the manufacturing process. Of the 19 million gallons of herbicides dispersed during the Vietnam War from 1962-1971, approximately 11 million gallons were Herbicide Orange, also called Agent Orange (9, 10).

The following table lists the names, periods of use, and compositions of the major herbicide mixtures used in the RVN (11):

Major Herbicides Used in Operation Ranch Hand

Code Name*	Period of Use	Formulation
Pink	1962-1964	2,4,5-T
Green	1962-1964	2,4,5-T
Purple	1962-1964	2,4-D; 2,4,5-T
Blue	1962-1971	Cacodylic acid
Orange, Orange II	1965-1970	2,4-D; 2,4,5-T
White	1965-1971	2,4-D; picloram

*Herbicide drums were identified by a circular band of paint colored in correspondence with these color codes

From the start, Operation Ranch Hand was heavily scrutinized because of the controversial nature of the program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The concerns were initially based on military, political, and ecological issues, but shifted to the issue of health in 1970. Claims of exposure to herbicides and dioxin, particularly to Agent Orange, and perceived adverse health effects among U.S. military service personnel resulted in substantial controversy and, eventually, class-action litigation. Since 1970, governmental agencies, universities, and industrial firms have funded numerous human and animal studies of dioxin effects.

In October 1978, the Air Force Deputy Surgeon General made a commitment to Congress and the White House to conduct a health study on the Operation Ranch Hand population. This population was comprised of aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The Surgeon General tasked the U.S. Air Force School of Aerospace Medicine at Brooks Air Force Base, Texas, to develop a study protocol. In 1982, after extensive peer review, the study protocol was published (1) and the epidemiological study began, designated the Air Force Health Study. The Brooks City-Base organizations responsible for executing the protocol have been reorganized and renamed several times since 1982. Currently, the Air Force Research Laboratory, Human Effectiveness Directorate, is responsible for the technical aspects of the study, and the 77th Aeronautical Systems Group is responsible for program management.

In 1987, when serum dioxin assay became available, the Air Force entered into a collaborative effort with the Centers for Disease Control and Prevention (CDC) to measure the serum dioxin levels in the AFHS population. The results of that effort demonstrated that substantially elevated levels of dioxin could still be found in the serum of some Ranch Hands (12, 13). Studies of serum dioxin levels have suggested that of all the military personnel who served in the RVN, the Ranch Hand cohort was one of the most highly exposed to herbicides containing dioxin (14). If herbicides caused an adverse health effect, then, based on the principle of dose-response, the Ranch Hands should manifest more or earlier evidence of adverse health.

1.3. AFHS DESIGN

For the baseline examination, the population ascertainment process identified 1,264 Ranch Hand personnel, living and deceased, who served in SEA between 1962 and 1971. Comparison veterans flew primarily transport missions in SEA during the same time that the Ranch Hand unit was active. Their units used C-130 transport planes flown and serviced by crews with similar training and background as those of Ranch Hand veterans. While Ranch Hand veterans spent most of their SEA service in the RVN, Comparison veterans spent on average less than 30 percent of their SEA service in the RVN and were stationed mostly in Guam, Japan, the Philippines, Taiwan, and Thailand. These Comparison veterans

may have been stationed in one, but usually in at least two countries; many had repeated tours of duty in SEA.

A computerized selection procedure identified Comparisons with similar characteristics to each Ranch Hand veteran. Comparisons were matched to a Ranch Hand based on age, race, gender, and military occupation (officer-pilot, officer-navigator, officer-other, enlisted flyer, and enlisted groundcrew). As many as 10 Comparisons were identified for each Ranch Hand. The purpose of identifying multiple Comparisons was an attempt to maintain the size of the Comparison group when a previously chosen Comparison declined to participate in a subsequent follow-up examination. Ranch Hands could not be replaced because the entire population was asked to participate. A protocol was established to describe the circumstances under which a Comparison was replaced and the method for replacement of Comparisons. An average of eight Comparison subjects were matched to each Ranch Hand.

1.4. AFHS STRENGTHS AND LIMITATIONS

In December 1999, Government Accounting Study (GAO) published a report describing the actions needed to improve communication of Ranch Hand data and results. This report recommended that more information on the limitations of the AFHS should be consistently emphasized in reports and other communication with AFHS customers. Below are the strengths and limitations of the study, as determined by AFHS investigators and the GAO.

- Strengths:
    - Participants had high level of compliance to the physical examinations
    - Long follow-up period
        - Six physical examinations over a 20-year period
    - Existence of a biomarker for exposure to dioxin and herbicides
    - Medical record verification of reported health conditions
    - Rigorous quality control
    - Adjustment for known confounding factors
    - Two-tiered management structure based on separate but parallel program management and technical (scientific/research) teams
    - Independently appointed and administered Advisory Committee
    - Periodic review by the National Academies of Science
- Limitations:
    - Small sample size for the detection of rare diseases (1,209 Ranch Hands eligible to participate in the first physical examination)
    - Dioxin measured long after service ended (last tour in 1971; first measurement in 1987)
    - Findings cannot be generalized to all Vietnam veterans
    - Possible incomplete adjustment for confounding factors

1.5. MORTALITY AND MORBIDITY COMPONENTS

The mortality component addressed noncombat mortality from the end of the qualifying SEA assignment. A baseline mortality review was conducted in 1982. Follow-up reports periodically updated mortality over the course of the AFHS. For the baseline mortality review and the first four mortality report updates, the study design was to five individuals were randomly selected from the matched Comparison set for each Ranch Hand for a 1:5 design as the study population. In 1987, the design was expanded to include all veterans, over 19,000, in the Comparison population; not all were matched to a Ranch Hand.

The morbidity component consisted of a baseline and five follow-up physical examinations. The baseline physical examination, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical conditions of interest found in the participants' external medical records. Information on reproductive outcomes also was collected. Each living Ranch Hand and a random living member of his Comparison set were selected to participate in the examination. The morbidity follow-up examinations comprised sequential questionnaires, medical records reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002. Participation was voluntary and each participant signed an informed consent form at the examination site.

For the baseline examination and the 1985 and 1987 follow-up examinations, the major focus of the analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the Comparisons (i.e., the unexposed cohort). It was not until February 1987 that methods to measure dioxin body burden in blood were available. During the 1987 physical examination, the Air Force began a collaborative study with the CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (12, 13, 15). The measurement of serum dioxin levels led to a statistical evaluation to assess dose-response relations between dioxin and health endpoints in 12 clinical areas. The 1987 examination was the first large-scale study of dose-response effects based on a direct measurement of dioxin. The statistical analyses evaluated the association between a specified health endpoint and dioxin among the Ranch Hands. The analyses also contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels (10 parts per trillion or less) of serum dioxin (5). The analysis of dose-response relations based on serum assays provided an important enhancement to AFHS.

In 1992, the fourth examination was initiated. The analysis focused on group differences between the Ranch Hand and Comparison cohorts and on the association of each health endpoint with serum dioxin levels. The fifth examination began in 1997, and the sixth and final examination began in 2002. As in 1992, the analyses in 1997 and 2002 focused on group differences between the Ranch Hand and Comparison cohorts and on the association of each health endpoint with extrapolated initial and 1987 serum dioxin levels (described in Chapter 2).

1.6. TYPES OF DATA COLLECTED

The types of data collected on participants included questionnaire data, medical records, physical examination and laboratory findings, and biological specimens. A baseline questionnaire, developed in 1982, remained the same for all six examinations. This questionnaire obtained information on demographics, education, occupation, medical history, study compliance, toxic exposures, and reproductive history. In general, responses to histories and other questions where the response did not change over time were obtained in the baseline questionnaire. A veteran who was new to the AFHS after 1982 completed the baseline questionnaire when he first participated in the study.

In examinations subsequent to the baseline examination, all participants were asked questions to update their histories since their last interviews. This questionnaire, known as the interval questionnaire, has remained essentially the same since its inception except for minor modifications. Thus, if a veteran participated in the AFHS for the first time in a follow-up examination (1985, 1987, 1992, 1997, or 2002), he was administered a baseline questionnaire to collect historical information through 1982 and an interval questionnaire to collect updates since 1982. Reported health conditions were confirmed by a review of external medical records and classified using International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes.

The physical examination included laboratory testing, physical examinations, psychological testing, and medical debriefings. The Air Force carefully prescribed the details of the examination in an examiner's handbook, given to each of the examining clinicians. Variations were neither desired nor authorized; Air

Force technical and contractual personnel reviewed all proposed examination procedural changes in detail prior to the start of the examinations. An important objective of the entire physical examination process was to ensure that bias was not created by any procedural change.

The requirement for the clinic staff to be "blinded" to the participant's group status (i.e., Ranch Hand, Comparison) was particularly stringent. The clinical staff was prohibited from knowing or seeking information as to the group identity of any participant. Additionally, participants were instructed not to divulge their group status to any of the staff members. At the end of his examination, each participant was asked to note on the evaluation form whether any member of the clinical or paramedical staff sought such information. When necessary, but only rarely, the physician or technician involved was reminded to be more careful in his or her conversations.

As an additional measure to ensure adherence to the physical examination requirements and to act as an Air Force representative and advocate for the participants, an Air Force monitor was present at the examination site at all times. Among their responsibilities was the requirement to observe the physical examinations noting whether there were any variances from the specific examination requirements.

The examination content, as designed by the Air Force, emphasized detection of medical endpoints suspected of being associated with exposure to herbicides and dioxin. In each follow-up examination, the Air Force used findings from the previous examination to refine the next examination.

1.7. AFHS PARTICIPATION

Across the 20 years of examinations, participation in the AFHS has been considered excellent for a cohort of this size and age. For example, of the 777 Ranch Hands and 1,174 Comparisons who participated in the 2002 follow-up examination, 671 (86.4%) of the Ranch Hands and 811 (69.0%) of the Comparisons participated in all six examinations. The number of Ranch Hands and Comparisons who participated in each of the six examinations is provided below.

Group/Examination	1982	1985	1987	1992	1997	2002
Ranch Hand Veterans Eligible to Participate	1,209	1,199	1,188	1,149	1,102	1,043
Ranch Hand Participants	**1,046**	**1,017**	**996**	**953**	**870**	**777**
Percentage of Ranch Hands Who Participated Relative to Those Eligible to Participate	86.5%	84.8%	83.8%	82.9%	78.9%	74.5%
Comparison Participants	**1,223**	**1,292**	**1,298**	**1,280**	**1,251**	**1,174**
Total	**2,269**	**2,309**	**2,294**	**2,233**	**2,121**	**1,951**

In August 2006, a study described participant compliance across all six physical examinations (16). Although a multitude of factors may have influenced participation in the AFHS, this study classified them broadly as health, logistical, demographic, operational, or publicity factors. The study found the effects of group, race, military occupation, year of birth, dioxin level, and military commitment on AFHS compliance were generally consistent in all six examinations. The compliance rate was relatively similar for the 1982, 1985, 1987 and 1992 examinations. A larger decrease in the compliance rate was observed for the 1997 and 2002 follow-up examinations. The number of veterans who refused for health reason and who refused for logistical reasons increased for the 1997 and 2002 follow-up examinations. In the 1987 and later follow-up examinations, age was associated with refusal for health reasons. As expected, older veterans refused more often for health reasons than did younger veterans. Original Comparisons refused more often than Ranch Hands for logistical reasons. Associations between refusal for logistical reasons and military occupation, age and military commitment were generally based on associations

found within the original Comparison group. Compliance or noncompliance at the previous examination correctly predicted compliance or noncompliance at a particular examination between 88 percent (for the 2002 examination) and 93 percent (for the 1987 examination) of the time. Three reasons for refusal concerned dissatisfaction: dissatisfaction with the U.S. Air Force or the U.S. Government, dissatisfaction with the AFHS, or dissatisfaction with previous AFHS examinations. More than 70 percent of the dissatisfaction reasons provided across all examinations were based on dissatisfaction with the U.S. Air Force or the U.S. Government. The study concluded that the loss of power because of declining participation as the AFHS progressed was expected and did not appear to have compromised the validity of the AFHS. The loss of power because of declining participation, however, generally was smaller than the loss of power that would have occurred if a replacement strategy had not been used. The replacement strategy succeeded in its attempts to prevent a large decrease in the number of Comparisons that participated in the AFHS.

1.8. EPIDEMIOLOGICAL AND STATISTICAL CONCEPTS USED IN THIS REPORT

Certain epidemiological and statistical principles were used throughout this report to determine what health effects may be attributed to occupational exposure to herbicides. The concepts of dose-response relation, biological plausibility, causal relationships, and clinical versus statistical significance are defined below.

A dose response relation is the relation between the amount of exposure to dioxin (dose) and the resulting changes in body function or health (response). Biological plausibility is a causal association, or a relationship between two factors, consistent with existing medical knowledge. A causal relationship is a link between two things in which one event occurs because of another event. For a causal relationship to exist there needs to be a distinct and factual link between an initial event and its result.

Statistical significance relates to the question of whether the results of a statistical test meet an accepted criterion level (standard p-value < 0.05). Statistical significance is a function of many factors, including the magnitude of the difference in a measure of health between Ranch Hands and Comparisons or, alternatively, the magnitude of the association between a measure of health and dioxin. Other factors that can influence statistical significance are the sample size, the reliability of the effect, and the reliability of the measurement instrument. A small p-value may be due to a large sample size or very little variability in the health measure. Clinical significance is a measure of whether a result is important in medical practice. While research results are often assessed through objective tests that generate numerical scores, clinical significance is often assessed through subjective measures, such as the impressions of a medical professional and the results of a medical test regarding whether a participant has been harmed by exposure.

1.9. REPORT ORGANIZATION

This report is organized as follows:

- Chapter 1 (Introduction) explains the purpose of the report; provides summary background information on the AFHS; describes the study design; and discusses mortality and morbidity components, the types of data collected, statistics on AFHS participation, and the organization of this report.
- Chapter 2 (Measures of Exposure) describes the three basic methods used to quantify exposure to herbicides and dioxin applied during the course of the AFHS.
- Chapter 3 (Interpretive Considerations) discusses specific technical items and issues that may have affected the interpretations of results found in the AFHS reports and journal articles.

- Chapter 4 (Ranch Hand Findings in Relation to Illnesses Presumptively Recognized by the Department of Veterans Affairs as Agent Orange-Connected) describes findings in the AFHS population that correspond to the 12 conditions that the DVA presumed were related to exposure to herbicides, such as Agent Orange, among veterans serving in-country during the Vietnam War.
- Chapter 5 (Reproductive Outcomes) describes findings from reports and journal articles that study the health, survival, and reproductive outcomes of Ranch Hands.
- Chapter 6 (Mortality) presents the results of Ranch Hand mortality analyses.
- Chapters 7 through 18 present a summary of morbidity results and are organized by clinical area and generally further organized by health endpoint.

  Chapter 7: General Health Assessment
  Chapter 8: Cardiovascular Assessment
  Chapter 9: Dermatology Assessment
  Chapter 10: Endocrinology Assessment
  Chapter 11: Gastrointestinal Assessment
  Chapter 12: Hematology Assessment
  Chapter 13: Immunology Assessment
  Chapter 14: Neoplasia Assessment
  Chapter 15: Neurology Assessment
  Chapter 16: Psychology Assessment
  Chapter 17: Pulmonary Assessment
  Chapter 18: Renal Assessment

This report is written in a narrative format. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the conclusion section of each the clinical area chapter. To weigh and interpret the findings, the authors considered the consistency, dose-response patterns, and biological plausibility of the statistically significant findings, particularly in the conclusion sections of the clinical chapters (Chapters 7-18). When weighing the importance of significant findings and reporting interpretations, the authors considered consistency of results, dose-response patterns, and biological plausibility. Statistically significant results that did not meet these criteria, but were instead sporadic, isolated, or inconsistent, were given less emphasis.

If an association was found to be adverse to the Comparison group, no mention was made in the report. In addition, a statistically nonsignificant association between a dependent variable and a measure of dioxin exposure was discussed if pertinent.

For reports on the physical exams through 1992, statistical models that tested for interactions between dioxin exposure metrics and other covariates (such as age or rank) were considered when analyzing a particular dependent variable. When an interaction was significant, further tests on subgroups of participants (such as older subjects or those exposed to solvents) were performed. Significant findings from these subgroup analyses are included in this report when they meet other inclusion criteria listed above. Starting with the 1997 exam, a decision was made that the interaction models were not producing enough consistently informative information to warrant continuing with them, and analysis was restricted to a simpler set of four models containing main effects only.

Unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this report) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this report). Further discussions of this stratification based on the participants' tour of duty are in Chapter 2.

The lack of a particular finding does not prove that no association exists nor should the reader conclude that the study has proven there is no association between herbicide exposure and adverse health. Consistent with the protocol, study investigators continue to question the underlying assumptions of all analyses, explore new ways to analyze data, and collaborate with specialists to determine whether exposure to Agent Orange adversely affected the health of Ranch Hand veterans.

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2. MEASURES OF EXPOSURE

2.1. INTRODUCTION

Throughout the 25 years of the AFHS, numerous techniques have been used in attempt to quantify exposure to herbicides. The classic method of comparing "exposed" and "unexposed" populations was termed "Group" analysis in the AFHS and was used in analyses of data from the baseline and all follow-up examinations. By the nature of this two-category classification, however, the magnitude of exposure within the exposed group was not quantified. In the reports based on data collected at the 1982, 1985, and 1987 examinations, an exposure index was constructed based on personnel records and herbicide spraying history. During the 1987 physical examination the Air Force collaborated with the CDC to measure dioxin levels directly in the serum of Ranch Hands and Comparisons (1-3). Data collected at the 1987, 1992, 1997, and 2002 follow-up examinations were analyzed using the serum dioxin measurement.

A summary of the measures of exposure used to analyze data from each examination is shown below:

Measure of Exposure/Examination	1982	1985	1987	1992	1997	2002
Group	X	X	X	X	X	X
Exposure Index	X	X	X			
Serum Dioxin Measurement			X	X	X	X

None of these methods was without controversy, and all methods had advantages and disadvantages. A background and discussion of these three methods are provided in more detail in this chapter. These methods of measuring exposure were used in analyzing mortality, reproductive outcome, and morbidity data.

2.2. GROUP STATUS

The exposed population, termed "Ranch Hand," was defined as individuals who were assigned to the U.S. Air Force organizations responsible for the aerial dissemination of herbicides and insecticides from C-123 aircraft in the RVN from 1962 through 1971. These individuals were identified from historical data sources (morning reports, military personnel records, and computer tapes) at the National Personnel Records Center, St. Louis, Missouri.

A review of all flying units present in SEA during the Vietnam War revealed that an absolutely ideal control group did not exist for the Ranch Hand population. Non-Ranch Hand crews flying and maintaining C-123 aircraft were considered as a comparison group, but the limited size of this population and the subsequent reconfiguration of these aircraft for transport and insecticide missions raised the possibility that this population might not truly be unexposed. Crewmembers of C-7 aircraft were considered, but the size of this population also was limited and these crewmembers served in the RVN after 1967 only. It finally was decided to use C-130 crewmembers stationed in SEA as the control group.

The Comparison population was defined as those individuals who were assigned to C-130 aircraft organizations in SEA during the same time as the Ranch Hands. Cargo-mission aircrew members and support personnel were selected because of sufficient population size and similar training and military background experiences to the Ranch Hand group. The Comparison population was not engaged in the

aerial spraying of herbicides or insecticides. Identification of this population was completed using similar methods to those used for the Ranch Hand group.

Ranch Hands and multiple Comparisons were matched by closest month of birth, race (Black versus non-Black), and military occupational code (categorized as officer-pilot, officer-navigator, officer-other, enlisted flyers, and enlisted groundcrew). Matching Ranch Hands and Comparisons on age attempted to account for the many clinical symptoms and signs associated with advancing age. Matching on race attempted to account for differences in chronic disease development. Military occupation was strongly associated with educational background and socioeconomic status.

As many as 10 Comparisons were identified for each Ranch Hand. The purpose of identifying multiple Comparisons was an attempt to maintain the size of the Comparison group when a previously chosen Comparison declined to participate in a subsequent follow-up examination. A declining study group size would lessen the ability to detect a statistical difference between Ranch Hands and Comparisons. Ranch Hands could not be replaced because the entire population was asked to participate. Comparisons, however, could be replaced. A protocol was established to describe the circumstances under which a Comparison was replaced and the method for replacement.

Analyses contrasting the Ranch Hand and Comparison cohort were straightforward, easy to interpret, and well established in epidemiological studies when a better measure of exposure is not available. Ranch Hands were "exposed" in these analyses, and Comparisons "not exposed", without regard to the magnitude of the exposure or possible misclassifications.

Results of the dioxin assay, which are discussed in more detail later in this chapter, appeared to show a difference in measured dioxin levels among the three military occupational categories (officers, enlisted flyers, and enlisted groundcrew). As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast for the reports on the 1992, 1997, and 2002 follow-up examinations. These contrasts compared Ranch Hands and Comparisons within the three military occupational categories. As discussed below, the median levels of exposure to dioxin among Ranch Hands were highest for enlisted groundcrew, followed by enlisted flyers, then officers.

2.3. ORIGINAL AFHS EXPOSURE INDEX

The exposure index as originally described in the AFHS protocol was used for the analysis of data collected at the 1982 baseline, 1985 follow-up, and 1987 follow-up examinations. The exposure index was related to the dioxin-containing herbicides: Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green. Archived samples of Herbicide Purple suggested that the material had an average dioxin concentration of approximately 33 parts per million (ppm) and Herbicide Orange had an average concentration of 2 ppm. Herbicides Pink and Green contained twice the dioxin of Herbicide Purple and, therefore, have been estimated to contain dioxin at a concentration of approximately 66 ppm (4, 5).

The exposure index used, E_i, specific to each Ranch Hand subject i, was $E_i = W*G_i/N_i$, where

W = dioxin weighting factor

G_i = gallons of dioxin-containing herbicide sprayed in the RVN theater during the i^{th} subject's tour of duty, and

N_i = number of Airmen with subject's duties in the Vietnam theater during the i^{th} subject's tour of duty.

The exposure index, therefore, was directly related to the amount of dioxin-containing herbicide sprayed and inversely related to the number of airmen with similar duties.

The dioxin-weighting factor was 24 or 1, depending on whether the material sprayed was sprayed before or after 1 July 1965. The weighting factor of 1 was used for the period after 1 July 1965, as documentation showed that only Herbicide Orange was disseminated by Air Force-flown, fixed-wing aircraft at that time. Prior to 1 July 1965, a combination of Herbicides Green, Pink, and Purple were sprayed by Air Force personnel in the RVN. After analysis of the data and normalization to Agent Orange concentrations, a weighting factor of 24 was established.

Herbicides Blue and White were sprayed during these time periods, but did not contain dioxin and, therefore, were not used in determining a dioxin-weighting factor.

The dates of each subject's tour(s) of duty in the RVN were determined by a review of military records. Records and reports were used to construct a table of gallons of dioxin-containing herbicide sprayed for each month during Operation Ranch Hand. Only fixed-wing spray missions were used because Ranch Hand personnel were not involved with helicopter and other spraying, such as from a backpack. The tour dates and the amount sprayed were combined to estimate the gallons of dioxin-containing herbicide sprayed in the RVN theater during the i^{th} subject's tour of duty.

The number of Ranch Hands with the subject's duties in the Vietnam theater during the i^{th} subject's tour of duty was determined relative to the five military occupational categories: officer-pilot, officer-navigator, officer-other, enlisted flyers, and enlisted groundcrew. For the purposes of analysis, the first three categories were combined into a single category called "officers." Navigators and pilots were exposed in the same manner, and other officers were administrators whose exposure was considered effectively zero. In addition, all administrative personnel in the enlisted groundcrew category were assigned a zero exposure value. The number of Ranch Hand airmen in each of the three categories—officer, enlisted flyers, and enlisted groundcrew—was used in calculating the exposure index.

2.4. SERUM DIOXIN MEASUREMENT

At the 1987 physical examination, the Air Force initiated a collaborative study with the CDC to measure dioxin levels in Ranch Hands and Comparisons (1-3). The results of that effort demonstrated that substantially elevated levels of dioxin could still be found in the serum of some Ranch Hands (1, 2). Studies of serum dioxin levels have suggested that of all the military personnel who served in the RVN, the Ranch Hand cohort was one of the most highly exposed to herbicides (6). If dioxin caused an adverse health effect, then, based on the principle of dose-response, the Ranch Hands should manifest more or earlier evidence of adverse health.

The analysis of dose-response relations based on serum assays provided an important enhancement to the previous AFHS investigations. This was the first large-scale study of dose-response effects based on a direct measurement of dioxin.

At the 1992, 1997, and 2002 follow-up examinations, attempts were made to determine dioxin levels for new subjects and those who were not previously measured at the 1987 follow-up examination. In addition, serum samples were taken from selected Ranch Hands at these examinations to provide insight on dioxin levels and the elimination of dioxin from the body.

The measurement of serum dioxin levels led to a statistical evaluation that assessed dose-response relations between dioxin and health endpoints in 12 clinical areas. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands. The analyses also contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels (10 parts per trillion [ppt] or less) of serum dioxin (7). In particular, three measures of dioxin were used, referred to as initial dioxin, categorized dioxin, and 1987 dioxin.

The correlation between the original AFHS exposure index and serum dioxin levels was described in the dioxin analysis of the 1987 physical examination results (7). The original exposure index was an indirectly calculated measure derived solely from personnel records and historical information. The serum dioxin level was used as a measure of exposure, and dioxin levels in Ranch Hands appeared to be placed logically relative to cohorts from other dioxin studies. In general, the relation between the measures of dioxin and the original AFHS exposure index showed weak associations between these alternative measures of exposure. The analysis reflected the high percentage of veterans who would be misclassified with regard to dioxin level if the original AFHS exposure index were assumed as the standard. For example, 77 of 287 (26.8%) Ranch Hand veterans in the original AFHS high exposure index category had dioxin levels less than 9ppt.

2.4.1. Initial Dioxin Model

The relation between a health endpoint and an extrapolated initial dioxin measure was examined for Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. Data on 213 Ranch Hand veterans with dioxin measured in blood collected in 1982, 1987, 1992, and 1997 produced a half-life estimate of 7.6 years (8); this estimate was used to extrapolate the 1987 dioxin level back in time to the end of the tour of duty that qualified a Ranch Hand veteran for inclusion in this study. If a Ranch Hand did not have a 1987 dioxin level, then the first dioxin measured, either at the 1992, 1997, or 2002 physical examination, was used to estimate the initial dioxin level. A statistical adjustment for body mass index at the time of the participant's measurement of dioxin was included in this model to account for body mass index-related differences in elimination rate (8).

Regardless of when the dioxin was measured, Ranch Hand veterans with a level less than or equal to 10 ppt were excluded from statistical analyses. Pharmacokinetic studies (8) were restricted to 343 Ranch Hand veterans with 1987 dioxin greater than 10 ppt because it was thought this value represented an upper threshold for background exposure (as evidenced by the fact that 10 ppt was the 98th percentile of the Comparison dioxin distribution) and that the ability to extrapolate using the half-life estimate did not hold at background levels.

2.4.2. Categorized Dioxin Model

The Ranch Hands for whom an initial dioxin was estimated were divided into two categories based on their initial dioxin measures. These two categories were referred to as "low Ranch Hand" and "high Ranch Hand". Two additional categories—Ranch Hands with serum dioxin levels at or below 10 ppt and Comparisons—were formed and included in the model. Ranch Hands with serum dioxin levels at or below 10 ppt were assigned to the "background Ranch Hand" category. If a Ranch Hand did not have a 1987 dioxin measurement, the first measured dioxin level was used. Another category was examined by combining the low and high Ranch Hand categories.

Consequently, four models and five categories were used in categorized dioxin analyses:

- Model 1: Comparisons
- Model 2: Background Ranch Hands (serum dioxin levels at or below 10 ppt)
- Model 3: Low Ranch Hands (serum dioxin levels greater than 10 ppt, category cutpoint based on initial dioxin level but varied by examination, cutpoint specified in the table below)
- Model 4: High Ranch Hands (serum dioxin levels greater than 10 ppt, category cutpoint based on initial dioxin level but varied by examination, cutpoint specified in the table below)
- Low and high Ranch Hands combined (serum dioxin levels greater than 10 ppt, all Ranch Hands included).

In 1987 and 1992 personality type A and B was used as a covariate for some of the analyses. The personality types were determined as the result of a Jenkins Activities Inventory administered to the participants.

The relation between the health endpoint in each of the four Ranch Hand models and the same health endpoint in the Comparison category was examined. As with analyses involving initial dioxin, a statistical adjustment for body mass index at the time of the participant's blood measurement of dioxin was included in the categorized model (8).

Whereas the extrapolated initial dioxin measure used dioxin in its continuous form for analysis, categorized dioxin inherently placed a participant in one of the four models provided below. Since 1987, the methods have been refined, the estimate of the half-life has been revised using additional data, the cohorts attending the follow-up examination have changed, and the nomenclature of the categories has changed. Below is a list of which participants are included in each of the dioxin categories for analysis of the 1987, 1992, 1997, and 2002 follow-up examinations:

Dioxin Category	1987 Follow-up Examination	1992 Follow-up Examination	1997 Follow-up Examination	2002 Follow-up Examination
Comparison	≤10 ppt measured dioxin level*	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level	All
Background (Ranch Hands)	≤10 ppt measured dioxin level**	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level
Low (Ranch Hands)	15 ppt<measured dioxin level≤33 ppt	measured dioxin level>10 ppt, initial dioxin≤143 ppt	measured dioxin level>10 ppt, initial dioxin≤94 ppt	measured dioxin level>10 ppt, initial dioxin≤118 ppt
High (Ranch Hands)	measured dioxin level>33 ppt	measured dioxin level>10 ppt, initial dioxin>143 ppt	measured dioxin level>10 ppt, initial dioxin>94 ppt	measured dioxin level>10 ppt, initial dioxin>118 ppt
Low and High (Ranch Hands)	measured dioxin level>15 ppt	measured dioxin level>10 ppt	measured dioxin level>10 ppt	measured dioxin level>10 ppt

*called "Background" in the 1987 follow-up examination report
**called "Unknown" in the 1987 follow-up examination report

2.4.3. 1987 Dioxin Model

The relation between the health endpoint and dioxin levels, as measured in 1987, was examined for all Ranch Hands with a dioxin measurement. If a Ranch Hand did not have a 1987 dioxin measurement, the first dioxin level obtained, either in 1992, 1997, or 2002, was extrapolated to the date of the 1987 physical examination. If the first dioxin level was not obtained in 1987 and was less than or equal to 10 ppt, it was not extrapolated to the 1987 level, but used at the measured value. This extrapolated dioxin measure was termed "current dioxin" in the 1987 and 1992 follow-up examination reports and "1987 dioxin" in the 1997 and 2002 follow-up examination reports.

When 1987 dioxin levels were examined for Comparisons, the vast majority of levels (approximately 98%) were below 10 ppt (9). The median 1987 dioxin level for Ranch Hands, however, was 11 ppt, and there was a distinct difference among military occupation categories. The median dioxin level was 24 ppt for enlisted groundcrew, 16 ppt for enlisted flyers, and 7 ppt for officers. The patterns within military occupation appeared to agree with Ranch Hand crew chief interviews regarding herbicide exposure conducted before the results of the first dioxin assay became available to AFHS participants (9).

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty in Vietnam that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this report) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this report).

Analyses performed using earlier and later tours of duty allowed investigation of the 1987 dioxin relation with health in relation to time. For example, if there were no relation between a measure of health and dioxin in the first few years after exposure, and a strong relation many years after exposure, there may be no association for Ranch Hands with later tours and an association for Ranch Hands with earlier tours. It is important to note that an effect of this kind could be due to the passage of time or to a higher initial dioxin level received by Ranch Hands with earlier tours, or both.

2.5. THE ORIGINAL AFHS EXPOSURE INDEX VERSUS SERUM DIOXIN MEASUREMENTS

As previously discussed (2.3) the first three AFHS reports, summarizing results of physical examinations conducted in 1982, 1985, and 1987, the potential relation between health endpoints and herbicide exposure in Ranch Hand veterans was assessed using the original AFHS exposure index.

The original AFHS exposure index was based on the untested assumption that the exposure of an individual decreased as the number of men available increased. The calculation was performed for each month of an individual's tour of duty, and the monthly results were summed to produce a single exposure index for each Ranch Hand veteran. Each veteran was then assigned to a low, medium, or high exposure category. These categories were of nearly equal size, and the cutpoints for these categories were different for the three military occupational categories (officer, enlisted flyer, or enlisted groundcrew).

Since 1987, all outcomes in this study were assessed with group contrasts and the dioxin body burden measured in serum as described in section 2.4. The 1987 results were analyzed twice, first using the original AFHS exposure index (12), and then using the dioxin body burden as the measure of exposure (7).

Both measures, the original AFHS exposure index and the serum dioxin measurement, have limitations. The exposure index was approximate in that the number of gallons sprayed used the totals across all bases rather than at a specific base. In addition, the assumption that exposure decreased as the number of men available increased may not have been reasonable. Interviews with Ranch Hand groundcrew in 1989 revealed that as the workload increased, more men were added to the job, resulting in more men becoming exposed rather than each man becoming less exposed. Finally, the spectrum of behaviors, skills, duties, weather-related work stoppages, work surges due to war conditions, and other factors (some known, some unknown) were not included in the calculation. For example, some Ranch Hand groundcrew had direct contact with bulk quantities of herbicide by filling the tanks and servicing the equipment, while others drove trucks or forklifts. The index did not distinguish between these two kinds of exposure patterns. In addition, some Ranch Hands were assigned solely to administrative duties. The original AFHS exposure index was defined as zero for those assigned to administrative duties.

The serum dioxin measurement is also limited as a measure of exposure. Although the half-life of dioxin is long (7.6 years), pharmacokinetic studies of Ranch Hand veterans suggested that the half-life varies with amount of body fat (8). Thus, some veterans may eliminate dioxin quickly and others more slowly. Variation of the dioxin half-life with body fat contributed to variation in the extrapolated initial dose at the time of exposure. In addition, more than 45 percent of Ranch Hand veterans had background levels, precluding extrapolation. Some of those with background levels may have had elevated levels while in the RVN, while others may not have been occupationally exposed at all. The exposure status of Ranch

Hands with background levels cannot be resolved with available data. Furthermore, no validated model exists to assess the adequacy of the estimated initial dose as an estimate of actual exposure among those with dioxin levels above background in 1987, 1992, 1997, or 2002. Use of serum dioxin measurements as a measure of exposure in the RVN is further confounded by the other possible sources of dioxin exposure. These sources include industrial exposure and environmental factors, such as burning of plastics and fish consumption.

The Ranch Hand Advisory Committee and the AFHS investigators thought the serum dioxin level was the most appropriate measure of exposure in this study because of the following:

- It was a direct measurement of the contaminant. (12)
- It was measured accurately (13)
- It correlated with reported skin exposure to herbicides among enlisted Ranch Hand veterans (10)
- Dioxin elimination in Ranch Hand veterans followed a plausible pharmacokinetic pattern (8)
- It was found to be plausibly associated with health conditions in this study and in other studies (14).

Throughout the 1987, 1992, 1997, and 2002 follow-up examination reports, dioxin levels were used as measures of both exposure to dioxin itself and exposure to dioxin-contaminated herbicides. Direct contrasts of Ranch Hand and Comparison veterans (group analyses) addressed the hypothesis of health effects attributable to any herbicide exposure experienced by Ranch Hand veterans during Operation Ranch Hand. Models involving dioxin measurements addressed the hypothesis that health effects change with the amount of exposure. Dioxin measurements were used as a measure of exposure to dioxin-contaminated herbicides because it was expected that as exposure to such herbicides increased, dioxin levels should increase. Therefore, the dioxin measurement served as a direct biomarker of exposure to dioxin-contaminated herbicides. No other direct measure or estimate of herbicide exposure was available with which to address hypothetical dose-response relations with health. Some indirect measures, such as self-report of skin contact among enlisted groundcrew, or simply being a Ranch Hand enlisted groundcrew member, are valuable alternatives because dioxin measures suggest that enlisted groundcrew experienced the heaviest exposures. Reported skin exposure was not addressed, but enlisted groundcrew status was addressed in contrasts of Ranch Hands and Comparisons. The use of dioxin as a measure of exposure to dioxin-contaminated herbicides was consistent with the goal of the study, which was to determine whether adverse health effects exist and can be attributed to occupational exposure to herbicides (15).

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3. INTERPRETIVE CONSIDERATIONS

3.1. INTRODUCTION

In interpreting results from any epidemiological study, no single result should be evaluated in isolation or out of context. Rather, interpretations should be addressed in the context of the overall study design, the data collection procedures, the data analysis methods, dose-response effects, strength of association, temporal relation, biological plausibility, and internal and external consistency. This especially applies to the AFHS. This effort was a long-term prospective study in which thousands of measurements and diagnoses were compiled on each participant. Those measurements and diagnoses were subjected to extensive statistical analyses, testing thousands of individual hypotheses. Each positive result should be scrutinized relative to findings in other studies, and relative to the statistical methods used and the medical and biological plausibility of the results. Conversely, the lack of a positive result only denotes that the null hypothesis of no association was not rejected. This has a very different conclusion than the possibly incorrect assertion that there is no effect. In addition, no epidemiological study can establish that there is no effect; i.e., that dioxin is safe (1). Critical considerations in the evaluation of results from this study are reviewed in this chapter.

3.2. STUDY DESIGN AND MODELING CONSIDERATIONS

Biased results will be produced if the assumptions underlying any of the statistical models are violated. As in any epidemiological study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis of no exposure effect because of possible exposure misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Dioxin data indicate that 45 percent of the Ranch Hands had only background serum dioxin levels. Either these Ranch Hands were never exposed or their initially elevated serum dioxin levels may have decreased to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether Ranch Hands who have background dioxin levels had elevated levels in the past because there was no method of measuring dioxin in blood prior to 1987 and because no blood was collected and saved prior to 1982.

Analyses of the association between health endpoints and extrapolated initial dioxin levels also are vulnerable to bias because they directly depend on two unvalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life. If dioxin elimination is first-order, but some Ranch Hands have a shorter half-life than others do, then there would have been misclassification of initial dioxin levels.

The half-life of dioxin was found to change with body mass index in 213 Ranch Hand veterans with up to four dioxin measurements, derived from serum drawn in 1982, 1987, 1992, and 1997 (2). The half-life increased with higher levels of obesity. A constant half-life was used in each report and was an estimate derived without adjustment for body mass index (2). As a partial solution to the observed relation between half-life and obesity, analyses using categorized dioxin or initial dioxin were adjusted for body mass index at the time of the blood measurement of dioxin. A study of dioxin elimination in 20 men exposed during the accident in Seveso, Italy, has validated the first-order model (3), which was the basis for the half-life estimate used in the AFHS. Validated models of dioxin elimination adjusted for body mass index or changes in body mass index, however, have not yet been derived.

To account for the possible misclassification of exposure between groups, the statistical model using categorized dioxin classified Ranch Hands into three levels of exposure: background, low and high levels of lipid-adjusted estimated initial dioxin. Each Ranch Hand dioxin category was contrasted with all Comparisons. Although this model depended less on the accuracy of the initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the classification of the Ranch Hands was subject to bias if the half-life and first-order dioxin elimination assumptions were not true. In addition, the Ranch Hands with background levels of lipid-adjusted serum dioxin may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels have decreased to background levels. This would result in a bias toward the null hypothesis of no dioxin effect on the health endpoint.

The model that analyzed the association between a 1987 dioxin measurement and health endpoints may be less subject to bias than other models that used dioxin as an exposure measure; however, recent dioxin levels may not be a good measure of exposure if serum dioxin elimination rates differed among individuals. Serum dioxin levels were extrapolated from 1992 measurements to 1987 for Ranch Hand veterans without serum dioxin levels measured in 1987. Serum dioxin levels also were extrapolated from 1997 measurements to 1987 for Ranch Hand veterans without levels measured in 1987 or 1992. In addition, serum dioxin levels were extrapolated from 2002 measurements to 1987 for Ranch Hand veterans without levels measured in 1987, 1992, or 1997. These extrapolations were performed only if the most recent measurement was greater than 10 parts per trillion (ppt). Therefore, these 1987 dioxin measurements were subject to bias from a possible violation of the half-life and first-order elimination assumptions that may affect the initial dioxin estimates. It was recognized that the serum dioxin level may have been greater than 10 ppt in 1987, but measurements taken from 1992, 1997, or 2002 may have been at 10 ppt or less and may eliminate individuals whose levels were above 10 ppt during the prior years, resulting in misclassification.

3.3. INFORMATION BIAS

Information bias, represented by the over- or under-reporting of disease symptoms, was minimized by verifying all diseases and conditions through a review of medical records. Conditions in Ranch Hands may be more verifiable because Ranch Hands may have been seen by physicians more often than Comparisons because of greater concern for their health. This would be revealed by group differences in the quantity and content of medical records. Because there was no way to quantify these aspects, this potential source of bias remains unexplored. This bias, if it existed, would affect only the models contrasting Ranch Hands and Comparisons (group analyses and categorized dioxin analyses). Information bias due to errors in the data introduced through data entry or machine error was negligible. All laboratory results were subject to strict quality control procedures, historical data were verified completely by medical records review, and medical data were subjected to strict quality control standards.

3.4. CONSISTENCY OF RESULTS

All statistically significant findings in the baseline and follow-up reports were subjected to clinical review, ensuring internal consistency throughout the report. In addition, these findings were compared to published results from other studies to ensure external consistency and articles were submitted to peer-reviewed journals.

3.5. STRENGTH OF ASSOCIATION

Although an association between a health outcome and either group or dioxin may be statistically significant (p-value<0.05), the association may not have clinical importance. The association may be weak, but statistically significant, because of the sample size or the prevalence of the condition. A strong adverse association between exposure and a disease condition, if it exists, would be revealed by an increased relative risk. Some authors have suggested that a statistically significant relative risk greater than 2.0 is cause for concern (4). Statistically significant relative risks less than 2.0 are generally considered less important than larger risks because relative risks less than 2.0 can arise more easily because of unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The weights of importance of the relative risk are epidemiological guidelines regarding analyses of association between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as extrapolated initial dioxin estimates or serum dioxin measurements).

The converse of this situation may also be true. A clinically important increase in a relative risk or a difference of means may not be statistically significant because of a lack of power. Statistical power may be an issue in a study with a population this size. A study with a population of the approximately 2,000 veterans who completed physical examinations lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma) because such events are unlikely to occur in large numbers in a group this small. While certain occupational toxicants have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) and are virtually nonexistent in the absence of the causative agent, other toxicants merely increase the risk of nondiagnostic pathology.

3.6. RESULTS BASED ON INDIRECT MEASURES OF THE VIETNAM EXPERIENCE AND HERBICIDE EXPOSURE

Interpretations of cohort contrasts in this study have been limited because, by design, both cohorts comprised veterans of the Vietnam War. Thus, the study was not designed to assess directly the SEA or Vietnam experience but rather the effect, if any, of occupational exposures to herbicides, with specific emphasis on Agent Orange, in Ranch Hand veterans relative to other Vietnam veterans who were not occupationally exposed. A "Vietnam" effect, if equally expressed by Ranch Hand and Comparison veterans, would not be detectable in this study.

The primary focus of this study was the potential effects of herbicide/dioxin exposure on health outcomes. The flexibility of the statistical methods and the comprehensive nature of the data collected, however, permitted the analysis of other factors, as allowed for in the AFHS protocol (5). Because it was impossible to know exactly the kind and amount of herbicide or other chemical exposures experienced during the Vietnam War by AFHS veterans, indirect measures of the Vietnam experience and herbicide exposure based on general knowledge of the Vietnam War, as derived from published accounts, have been considered. Morbidity analyses of cancer incidence, in which the Ranch Hand and Comparison cohorts were stratified by time spent in the SEA region and the percentage of SEA service spent in Vietnam, have been performed. Analyses of cancer incidence using the national population as a reference, with and without restriction to dates of tour, also have been conducted.

Analyses of this type demonstrated that effects not observed in the entire population might be seen in subgroups of AFHS veterans. In addition, analyses based on stratification by operational factors, rather than nonmedical risk factors, may yield results in certain subgroups. Stratification, however, can limit the ability to detect a difference because of the inherent reduction in sample size. The series of reports for the AFHS have focused on analyses based on standard epidemiological models that use known

medical and demographic risk factors, but additional analysis on subpopulations with alternative risk factors may yield different results.

3.7. BIOLOGICAL PLAUSIBILITY

The assessment of biological plausibility requires consideration of a biological mechanism relating the exposure and effect of interest. While a lack of biological plausibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological explanation of results must be interpreted with caution. In the AFHS, statistically significant results were subjected to medical review and comparison with previously published results to identify consistent and biologically plausible results.

3.8. INTERPRETATION OF NONSIGNIFICANT RESULTS

In this study, a lack of significant results relating dioxin to a particular disease only means that the study was unable to detect a relation between herbicides or dioxin and health. This does not imply that a relation may not exist, but that if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relation between dioxin and health. The AFHS was not designed to establish safety; rather, it was designed to determine whether a hazard existed for the exposed personnel. Determining safety would require a study at least 10 times as large, as determined in a 1985 study presenting minimal sample size criteria for proof of safety and hazard in studies of environmental and occupational exposures (1).

3.9. EXTRAPOLATION TO ARMED FORCES GROUND TROOPS

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is problematic because Ranch Hand and ground troop exposure situations were very different from one another. Based on serum dioxin testing results obtained by the CDC (7) and others (8), nearly all ground troops tested had 1987 levels of dioxin similar to background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had 1987 dioxin levels similar to those in men who never left the United States (with average dioxin levels of 4.2 ppt and 4.1 ppt, respectively). Little scientific basis for an extrapolation of these results to the larger population of Vietnam veterans exists. The possibility that a limited number of veterans could have been exposed to levels of dioxin comparable to the Ranch Hand veterans cannot be excluded, but because blood or adipose tissue were not collected immediately after their return from Vietnam, the actual exposures of these veterans cannot be known. Others may have received long-term low-dose exposure. These possibilities and a multitude of factors, including differential elimination and exposures to other persistent organic pollutants, suggest that existing data do not provide an adequate basis for extrapolation.

3.10. CONSIDERATIONS FOR SUMMARIZING RESULTS

A study of this scope with a multitude of endpoints demands, and at the same time defies meaningful summary tabulation. Such summaries can be misleading because they ignore correlations between the endpoints, correlations between examination results, and the nonquantifiable medical importance of each endpoint. In fact, some endpoints were indices developed from combining multiple endpoints. Other endpoints, such as psychological scales, may be highly associated with other similar endpoints. In addition, such tabulations combine endpoints that are not medically or biologically comparable. For example, diminished sense of smell may be of less medical importance than the presence of a malignant neoplasm. Summaries can be misleading and must be interpreted carefully—an elementary tally of significant, or nonsignificant, results is not appropriate.

3.11. METHODS FOR DRAWING CONCLUSIONS

Numerous dependent variables were considered because of the lack of a predefined medical endpoint. Each dependent variable was analyzed in many different ways to accommodate covariate information and different statistical models. In the hypothetical case when a Ranch Hand adverse health outcome was not related to exposure group or dioxin, about 5 percent of the results would be false positive. Observing significant results due to multiple testing, even when there was no relation between exposure group or dioxin and health, is known as the multiple-testing artifact and is common in large studies. Unfortunately, there is no statistical procedure available to distinguish between those statistically significant results that arise due to the multiple testing artifact and those that may be due to a bona fide dioxin effect.

To weigh and interpret the findings, the authors considered the consistency, dose-response patterns, and biological plausibility of the statistically significant findings, particularly in the Conclusion sections of the clinical chapters (Chapters 7-18). Consistency, dose-response patterns, and biological plausibility have been discussed previously in this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis.

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4. RANCH HAND FINDINGS IN RELATION TO ILLNESSES PRESUMPTIVELY RECOGNIZED BY THE DEPARTMENT OF VETERANS AFFAIRS AS AGENT ORANGE-CONNECTED

4.1. INTRODUCTION

Congress directed the Secretary of Veterans Affairs in Public Law 102-4, signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam War. In 1994, the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides published its first report (1). This report classified evidence of an association between a health problem and exposure to herbicides as "sufficient evidence of an association", "limited/suggestive evidence of an association", or "inadequate/insufficient evidence to determine whether an association exists", or "limited or suggestive evidence of no association." The evidence regarding association was drawn from occupational, environmental studies, and studies of veterans in which individuals were exposed to the herbicides used in Vietnam, to their components, or to their contaminants. Since this report, the IOM has published five biennial updates—1996, 1998, 2000, 2002, and 2004—incorporating results from additional studies (2-6). The work of this Committee has provided the DVA with information to create the list of service-connected conditions described below.

Any veteran who served in Vietnam between January 9, 1962, and May 7, 1975, and has one or more of the following conditions is presumed by the DVA to have been exposed to Agent Orange, and, therefore, presumptively recognized that his condition is service-connected (7-9):

- Time-dependent conditions:
    - Acute and subacute transient peripheral neuropathy (must appear within 1 year of exposure and resolve within 2 years of date of onset)
    - Chloracne (must occur within 1 year of exposure)
    - Porphyria cutanea tarda (PCT) (must occur within 1 year of exposure)
- Rare conditions:
    - Chronic lymphocytic leukemia
    - Hodgkin's disease
    - Multiple myeloma
    - Non-Hodgkin's lymphoma
    - Soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma)
    - Spina bifida (except spina bifida occulta) (in children of Vietnam veterans born after the veteran's tour in Vietnam)
- Common conditions:
    - Prostate cancer
    - Respiratory cancers, including cancers of the lung, larynx, trachea, and bronchus

- Type 2 diabetes.

Findings from the AFHS for these conditions are described in the remainder of this chapter. Descriptions of each of these conditions have been taken from the April 2005 Veterans Affairs' *Agent Orange Review* (9). The term "compound of interest" in the discussions includes 2,4-D, 2,4,5-T and its contaminant dioxin, cacodylic acid, and picloram. Relative risks (RR) were calculated specifically for this chapter for some of the compensable conditions based on AFHS data through January 2006. The population used was 1,197 Ranch Hands and 1,855 Comparisons who were either partially or fully compliant in the AFHS. Partially compliant participants only completed the in-home interview and questionnaire while fully compliant participants attended one or more of the AFHS physical examination.

4.2. TIME-DEPENDENT CONDITIONS

Medical records were examined to verify all conditions for Ranch Hand and Comparison participants. Special emphasis was given to the identification of time-dependent conditions, that is, conditions that would have occurred only shortly after exposure (acute or subacute transient peripheral neuropathy, chloracne, or PCT).

4.2.1. Acute and Subacute Transient Peripheral Neuropathy

Peripheral neuropathy is a nervous system condition that causes numbness, tingling, and muscle weakness. This condition affects only the peripheral nervous system, that is, the nervous system outside the brain and spinal cord. Only the transient (short-term) acute and subacute forms of this condition, not the chronic persistent forms, have been associated with herbicide exposure (9).

No Ranch Hands or Comparisons were observed with acute or subacute transient peripheral neuropathy in the AFHS.

In the 1996 *Veterans and Agent Orange* update (2), the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there is "limited/suggestive evidence of an association" between exposure to certain herbicides used in Vietnam and the development of early onset (previously termed "acute and "subacute") transient peripheral neuropathy. This conclusion remained unaltered in the 2004 *Veterans and Agent Orange* update (6). In this report, however, the Committee added that there was inadequate or insufficient "evidence to determine an association between exposure to compounds of interest and delayed or persistent peripheral neuropathy."

4.2.2. Chloracne

Chloracne is a skin condition that is considered a hallmark sign of dioxin exposure. Typically, acne-like lesions will develop over the eyes, ears, and neck but can occur in the groin area as well the armpits. It occurs shortly, days to weeks, after a high exposure to the chemical. Chloracne can resolve within two years or persist for decades.

No Ranch Hands or Comparisons were observed with chloracne in the AFHS, and no medical records identified the presence of chloracne in any of the Ranch Hand participants. Furthermore, no biopsies to confirm the diagnosis of chloracne were deemed necessary by the examining dermatologists at the physical examinations.

In the first *Veterans and Agent Orange* report in 1994, published by the IOM, the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there was "sufficient evidence of an association" between exposure to dioxin and chloracne (1). This conclusion remained unaltered in the 2002 *Veterans and Agent Orange* update (5); however, the Committee added a notation that chloracne would appear shortly after dioxin exposure and not after a long latency. The 2004 *Veterans and Agent Orange* update concurred with previous reports (6).

4.2.3. Porphyria Cutanea Tarda (PCT)

PCT is a disorder characterized by liver dysfunction and by thinning and blistering of the skin in sun-exposed areas.

No Ranch Hands or Comparisons was observed with PCT in the AFHS.

The IOM Committee, as reported first in their 1994 book on the health effects of herbicides used in Vietnam (1), concluded that there was "sufficient" evidence to establish an association, although not a causal relation between herbicides or dioxin and PCT. In the 1996 report, the association with PCT was downgraded from "sufficient" to "suggestive" evidence, based on studies completed since the first IOM report (2). The 2004 *Veterans and Agent Orange* update continued to support a finding of "limited/suggestive" evidence between herbicides and PCT (6).

4.3. RARE CONDITIONS

4.3.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is a disease that progresses slowly with increasing production of excessive numbers of white blood cells.

Five Ranch Hands and six Comparisons had chronic lymphocytic leukemia (relative risk [RR] = 1.2, 95% confidence interval [C.I.]: [0.4,4.0]). Three of the Ranch Hands with chronic lymphocytic leukemia were in the background dioxin category (RR = 1.7, 95% C.I.: [0.4,6.7]), one of the Ranch Hands was in the low dioxin category (RR = 0.9, 95% C.I.: [0.1,7.7]), and one Ranch Hand did not have a dioxin measurement. The six Comparisons with chronic lymphocytic leukemia had a measured dioxin level less than 10 ppt.

In 2004, the AFHS staff and colleagues published a journal article related to cancers of the lymphopoietic system, where lymphomas, multiple myeloma, and leukemia were combined because of a sparse number of occurrences (10). No adverse effects to Ranch Hands were noted in this analysis.

In the 2004 *Veterans and Agent Orange* update, the epidemiologic evidence was considered by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides to be "sufficient" concerning chronic lymphocytic leukemia, and "exposure to at least one compound of interest (6)."

4.3.2. Hodgkin's Disease

Hodgkin's disease is a malignant lymphoma characterized by progressive enlargement of the lymph nodes, liver, and spleen, and by progressive anemia.

One Ranch Hand and three Comparisons had Hodgkin's disease (RR = 0.7, 95% C.I.: [0.1,8.2]). The Ranch Hand with Hodgkin's disease was in the background dioxin category (RR = 1.7, 95% C.I.: [0.1,18.4]). The three Comparisons with Hodgkin's disease had a measured dioxin level less than 10 ppt. One Comparison was diagnosed with Hodgkin's disease during his tour of duty in SEA and was excluded from the analysis.

The IOM Committee, as reported in the first *Veterans and Agent Orange* book in 1994 on the health effects of herbicides used in Vietnam, concluded that there was "sufficient" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of Hodgkin's disease (1). The 2004 *Veterans and Agent Orange* update stated that an association existed between exposure to at least one of the compounds of interest and Hodgkin's disease (6).

4.3.3. Multiple Myeloma

Multiple myeloma is a cancer of specific bone marrow cells characterized by bone marrow tumors in various bones of the body.

Four Ranch Hands and one Comparison had multiple myeloma (RR = 5.6, 95% C.I.: [0.6,50.5]). One of the Ranch Hands with multiple myeloma was in the background dioxin category (RR = 2.9, 95% C.I.: [0.2,46.7]) and three were in the low dioxin category (RR = 17.1, 95% C.I..: [1.8,164.9]). The one Comparison with multiple myeloma had a measured dioxin level less than 10 ppt.

The evidence for an association, although not a causal relation, between dioxin exposure and the occurrence of multiple myeloma was considered "limited/suggestive" by the IOM Committee in the first *Veterans and Agent Orange* report and all updates through 2004 (1-6).

4.3.4. Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is a group of malignant tumors that affect the lymph glands and other lymphatic tissue.

Three Ranch Hands and 11 Comparisons had non-Hodgkin's lymphoma (RR = 0.4, 95% C.I.: [0.1,1.5]). Two of the Ranch Hands with non-Hodgkin's lymphoma were in the background dioxin category (RR = 0.7, 95% C.I.: [0.1,3.0]) and one was in the high dioxin category (RR = 0.5, 95% C.I..: [0.1,4.1]). Ten of the 11 Comparisons with non-Hodgkin's lymphoma had a measured dioxin level; 2 of these 10 Comparisons had a measured dioxin level greater than 10 ppt.

The IOM Committee, as reported first in the 1994 book on the health effects of herbicides used in Vietnam (1), concluded that there was "sufficient" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of non-Hodgkin's lymphoma. In the 2004 *Veterans and Agent Orange* update, the Committee concluded there was "sufficient" evidence to conclude that an association existed between exposure to at least one compound of interest and non-Hodgkin's lymphoma (6).

4.3.5. Soft Tissue Sarcoma (Other than Osteosarcoma, Chondrosarcoma, Kaposi's Sarcoma, or Mesothelioma)

Soft tissue sarcoma is a group of different types of malignant tumors that arise from body tissues, such as muscle, fat, blood and lymph vessels, and connective tissues (not in hard tissue, such as bone and cartilage). These cancers are in the soft tissue of and between organs.

Two Ranch Hands and four Comparisons had a soft tissue sarcoma (RR = 0.7, 95% C.I.: [0.1,4.1]). One of the two Ranch Hands with a soft tissue sarcoma was in the high dioxin category (RR = 1.3, 95% C.I.: [0.1,11.9]); the other Ranch Hand did not have a dioxin measurement. All four Comparisons with a soft tissue sarcoma had a measured dioxin level; one of these four Comparisons had a measured dioxin level greater than 10 ppt.

The IOM Committee, as reported first in the 1994 book on the health effects of herbicides used in Vietnam (1), concluded that there was "sufficient" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of soft tissue sarcoma. This conclusion has remained unchanged in all *Veterans and Agent Orange* updates through 2004 (2-6).

4.3.6. Spina Bifida (except Spina Bifida Occulta) (in Children of Vietnam Veterans)

Spina bifida is a neural tube birth defect that results from the failure of the bony portion of the spine to close properly in the developing fetus during early pregnancy.

Among 792 live-born infants to Ranch Hand fathers and 981 live-born infants to Comparison fathers (these are individuals with serum dioxin levels), four children from Ranch Hand fathers and zero children

from Comparison fathers had spina bifida or anencephaly, which are both neural tube defects (11). Two of the Ranch Hands were in the low dioxin category and two were in the high dioxin category (12).

This result, along with two other epidemiological studies, led the IOM to conclude that there was "limited/suggestive evidence of an association" between exposure to herbicides and spina bifida in the offspring of exposed individuals, as reported in the 1996 *Veterans and Agent Orange* update (2). This conclusion remained the same in subsequent *Veterans and Agent Orange* updates in 1998, 2000, 2002, and 2004 (3-6).

4.4. COMMON CONDITIONS

4.4.1 Prostate Cancer

Sixty-three Ranch Hands and 93 Comparisons had prostate cancer (RR = 1.0, 95% C.I.: [0.7,1.4]). Of the 63 Ranch Hands with prostate cancer, 25 Ranch Hands were in the background dioxin category (RR = 0.8, 95% C.I.: [0.5,1.3]), 27 were in the low dioxin category (RR = 1.5, 95% C.I..: [0.9,2.2]), 10 were in the high dioxin category (RR = 0.8, 95% C.I.: [0.4,1.6]), and 1 Ranch Hand did not have a dioxin measurement. Of the 93 Comparisons, 90 had a measured dioxin level, and 1 of these 90 Comparisons had a measured dioxin level greater than 10 ppt.

The examination reports showed no consistent relationship between prostate cancer and dioxin. Several journal articles (13-15) were written on prostate cancer. The incidence of prostate cancer was increased among white Ranch Hands and Comparisons veterans based on data through the 1997 examination. Furthermore, this study found among veterans who spent at most 2 years in SEA, the risk of prostate cancer was increased in the high dioxin category. A study (14) just looking at prostate cancer in Comparisons found that service in SEA was itself a risk factor for prostate cancer in AFHS Comparisons, independent of dioxin exposure. Another study (15) found for participants that attended at least one of the six examinations and who had a dioxin level there was no overall increase in the risk of prostate cancer in Ranch Hands versus the Comparisons. No increase risk of prostate cancer was observed within Ranch Hand group in association with dioxin or time served in SEA. However, in Comparisons time served in SEA was associated with an increased risk of prostate cancer.

The IOM Committee concluded that there was "limited/suggestive" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of prostate cancer in the first *Veterans and Agent Orange* report and all updates though 2004 (1-6).

4.4.2. Respiratory Cancers, Including Cancers of the Lung, Larynx, Trachea, and Bronchus

Forty-four Ranch Hands and 58 Comparisons had respiratory cancer (RR = 1.1, 95% C.I.: [0.7,1.6]). Of the 44 Ranch Hands with respiratory cancer, 14 Ranch Hands were in the background dioxin category (RR = 1.1, 95% C.I.: [0.6,2.0]), 14 were in the low dioxin category (RR = 1.4, 95% C.I..: [0.8,2.6]), 2 were in the high dioxin category (RR = 0.3, 95% C.I.: [0.1,1.1]), and 14 Ranch Hands did not have a dioxin measurement. Of the 58 Comparisons, 41 had a measured dioxin level, and one of these 41 Comparisons had a measured dioxin level greater than 10 ppt.

The evidence for an association, although not a causal relation, between dioxin exposure and the occurrence of respiratory cancers was considered "limited/suggestive" by the IOM Committee through 2004 (1-6).

4.4.3. Type 2 Diabetes

Type 2 diabetes, or diabetes mellitus, is characterized by high blood sugar levels resulting from the body's inability to respond properly to the hormone insulin.

One hundred and ninety Ranch Hands and 308 Comparisons had type 2 diabetes (RR = 0.9, 95% C.I.: [0.8,1.1]). Of the 190 Ranch Hands with type 2 diabetes, 50 Ranch Hands were in the background dioxin category (RR = 0.6, 95% C.I.: [0.5,0.9]), 60 were in the low dioxin category (RR = 1.0, 95% C.I.: [0.7,1.3]), 70 were in the high dioxin category (RR = 1.2, 95% C.I.: [0.9,1.6]), and 10 Ranch Hands did not have a dioxin measurement. Of the 308 Comparisons with type 2 diabetes, 292 had a measured dioxin level, and 9 of these 292 Comparisons had a measured dioxin level greater than 10 ppt.

Results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent adverse relation between dioxin levels and diabetes. Although the prevalence of diabetes was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. Increased risks of diabetes were found with initial dioxin, in the high dioxin category, and with 1987 dioxin levels. An increase in severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and hemoglobin A1c also were observed as initial and 1987 dioxin levels increased.

The journal articles (16-23) showed glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased, and time-to-diabetes-onset decreased with dioxin exposure. Serum insulin abnormalities for Ranch Hands in the high dioxin category were increased in nondiabetics. Most of the significant relative risks described in the reports were less than 2.0. In the small matched pairs study (23), it was estimated that an 18-fold increase in dioxin would be associated with a 10 percent change in the insulin sensitivity index.

Epidemiologic studies suggested that any increased risk of type 2 diabetes from herbicide or dioxin exposure was small when compared to the known predictors—family history, obesity, physical inactivity—for diabetes. Based on its comprehensive review of the literature, the IOM found "limited/ suggestive evidence of an association" between exposure to herbicides, including 2,4,5-T and its contaminant dioxin, and type 2 diabetes (24). This conclusion remained unchanged in the 2002 and 2004 *Veterans and Agent Orange* updates.

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5. REPRODUCTIVE OUTCOMES

5.1. INTRODUCTION

The possibility of an increased risk in birth defects in children of Vietnam veterans had caused veterans, the public, and federal and state legislatures concern. Animal fertility studies in various species had shown variations of 2,4-D, 2,4,5-T and dioxin toxicity relative to age, dosage levels and routes of administration.

At the AFHS baseline examination in 1982, reproductive outcome information was collected and the results of the analysis of these data were included in the 1982 examination report. The data on fertility and reproductive events were based on data provided by participants and spouses/partners in separate questionnaires administered at the baseline examination and during in-home interviews. At the time of analysis for the 1982 reproductive outcome information, this self-reported information had not been verified with medical records. Starting in 1985, birth defects and neonatal deaths reported by study participants and their spouses/partners were verified by a review of birth and other medical records, birth certificates, and death certificates.

Semen was collected from the participants at the 1982 baseline examination and infertility, sperm count and abnormalities were analyzed.

Starting with the 1987 physical examination serum dioxin assays were drawn and subsequent analysis of reproductive outcomes relative to paternal serum dioxin levels were analyzed (2-4).

The analysis of reproductive outcomes of the AFHS population can be found in the following Air Force technical reports and journal articles. The first technical report (1) was the 1982 baseline examination report, which contained a section on reproductive outcomes based on spouse/partner-reported information. The second technical report (5) was written based on verified outcomes rather than self-reported information. The third technical report (4) presented the result of reanalysis based on verified information in conjunction with paternal serum dioxin levels.

- An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: baseline morbidity study results (1)
- An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: reproductive outcome update (5)
- An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: reproductive outcomes (4)

The following journal articles were written by AFHS researchers and their colleagues:

- Paternal serum dioxin and reproductive outcomes among veterans of Operations Ranch Hands (2)
- Paternal dioxin, preterm birth, intrauterine growth retardation, and infant death. (3).
- Letter to the editor: Paternal dioxin and the sex of children fathered by veterans of Operation Ranch Hand (6).

The 2004 IOM committee determined that there was inadequate or insufficient evidence to ‘determine an association between exposure to 2,4-D, 2,4,5-T, dioxin, picloram or cacodylic acid and altered hormone concentrations, semen quality, or infertility; spontaneous abortion; late-fetal, neonatal, or infant death;

low birthweight or preterm delivery; birth defects other than spina bifida; altered sex ratio; and childhood cancers. There was limited or suggestive evidence for an association between spina bifida and exposure to the compounds of interest." (7)

5.2. TECHNICAL REPORTS

5.2.1. 1982 Baseline Examination

The baseline report (1) analyzed 7,399 conceptions; 3,293 Ranch Hand–reported conceptions and 4,106 Comparison-reported conceptions. These figures reflected children born before and after the father's qualifying tour of duty in SEA.

Analysis revealed no difference between Ranch Hands and Comparisons for infertility, sperm count, or sperm abnormalities.

The conception outcomes of miscarriage, stillbirth, induced abortion, and live birth also were no different between spouses or partners of Ranch Hands and Comparisons. An association between increasing herbicide exposure and miscarriage was identified in Ranch Hand officers, but was not seen for other military occupations (i.e., enlisted flyers, enlisted groundcrew).

An increase in post-SEA live birth outcomes of physically handicapped, all birth defects, and neonatal death for children of Ranch Hands was found. An association between increasing herbicide exposure and birth defects was observed in Ranch Hand officers and enlisted flyers.

5.2.2. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides: Reproductive Outcome Update

This report (5) analyzed birth defects and neonatal deaths that were verified by medical records as of 15 September 1984 (approximately 60% of reported birth defects and approximately 80% of reported neonatal deaths) on Ranch Hand and Comparisons who attended the 1982 physical examination. The results found, based on this verified data, were comparable to the results of the self-reported data. There was a change in the relation between birth defects and group (i.e., Ranch Hand, Comparison), depending on whether the conception was prior to or after the father's service in SEA. More verified birth defects for conceptions prior to the father's service in SEA were found for Comparisons than for Ranch Hands, but more verified birth defects for conceptions after the father's service in SEA were found for Ranch Hands than for Comparisons.

A change also was indicated in the relation between neonatal deaths and group, depending on whether the death was prior to or after the father's service in SEA. The percentage of neonatal deaths was similar in Ranch Hands and Comparisons for births prior to the father's service in SEA, but after the father's service in SEA, more neonatal deaths occurred among the children of Ranch Hand fathers than of Comparison fathers.

5.2.3. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides: Reproductive Outcomes

This report (4) analyzed the reproductive outcomes of the 791 Ranch Hands and 942 Comparisons for whom dioxin levels had been determined by August 1991 and who had attended the 1982, 1985 or 1987 examinations. These men had fathered 5,489 pregnancies including 4,514 live births. This was a subset of all 1,098 Ranch Hands and 1,549 Comparisons who had fathered 8,263 pregnancies and 6,792 live births. All data had been verified by review of pertinent records. The health status of each child was verified through the age of 18. Analyses of miscarriage, total adverse outcomes, total conceptions, birth weight, birth defects, birth defect severity, specific birth defects, infant death, and neonatal death were carried out on all conceptions and children and with restriction to full siblings to minimize variation.

Additionally, all reproductive outcomes except sperm count, percent abnormal sperm and multiple birth defects were analyzed with and without consideration of the pre-SEA reproductive experiences of these men. Analyses were adjusted for as many as eight covariates; father's race, mother's smoking history during pregnancy, mother's drinking history during pregnancy, mother's age, father's age, time of conception relative to SEA tour, father's military occupation in SEA, and industrial chemical exposure.

This report found similar findings as the 1982 report; Ranch Hand rate of pre-SEA birth defects was less than the Comparison rate, and the Ranch Hand rate of post-SEA birth defects was greater than the Comparison rate. Additional analyses, however, indicated no relation between paternal dioxin levels (initial, categorized, or 1987 dioxin) and the differential rates of pre-SEA and post-SEA birth defects.

5.2.3.1. Sperm count and Morphology

No significant association was found between dioxin and sperm count or the percentage of abnormal sperm.

5.2.3.2. Miscarriages and Adverse Outcomes

Miscarriages and adverse outcomes increased with increasing 1987 dioxin in conceptions fathered by Ranch Hands with late tours of duty, but decreased with increasing 1987 dioxin in conceptions fathered by Ranch Hands with earlier tours of duty. It was concluded that the results were mixed and biologically implausible and appeared unrelated to dioxin.

5.2.3.3. Low Birth Weight

Among children born post-SEA, the rate of abnormally low birth weight in Ranch Hand children (93.3 per 1,000) was greater than that in children of Comparisons (41.9 per 1,000). This change was due as much to the decrease in the Comparison rate as to the increase in the Ranch Hand rate.

5.2.3.4. Birth Defects

Few associations were found between dioxin and 13 categories of birth defect (total congenital anomalies; nervous system anomalies; eye anomalies; ear, face, and neck anomalies; circulatory system and heart anomalies; respiratory system anomalies; digestive system anomalies; genital anomalies; urinary system anomalies; musculoskeletal deformities; anomalies of the skin; chromosomal anomalies; and, other and unspecified anomalies). Those associations that were noted, total congenital anomalies and musculoskeletal deformities, did not show increasing risks with increasing dioxin.

Major birth defects were defined, according to CDC definitions, as those defects that potentially can affect survival, result in marked physical or psychological handicaps, or interfere with a child's prospects for a productive and fulfilling life. No consistent patterns of association were found between the major birth defects and dioxin. In some analyses, the highest rates of major birth defects were found in children born to Ranch Hands with intermediate categorized dioxin levels, while the lowest rates were found in children born to Ranch Hands with the highest categorized dioxin levels. The results suggested no evidence that birth defect severity was adversely associated with dioxin.

Twelve specific birth defects (anencephaly, spina bifida, hydrocephalus, cleft palate, cleft lip/palate; esophageal atresia; anorectal atresia; polydactyly; limb reduction defects; hypospadias; congenital hip dislocation; and Downs syndrome) and four developmental disabilities (disruption of emotion specific to childhood and adolescence; hyperkinetic syndrome of childhood; specific delays in development; and mental retardation) were investigated. There were only enough occurrences to permit statistical analysis on specific delays in development and hyperkinetic syndrome.

5.2.3.5. Development Delays and Hyperkinetic Syndrome

Findings were few for both specific delays in development and hyperkinetic syndrome and often were in the direction opposite of an expected dose-response relation. For example, one was due to high post-SEA rates in children of Ranch Hands with intermediate dioxin levels and lower rates in children of Ranch Hands with high dioxin levels. These findings were considered weak, inconsistent, and often opposite to the expected dose-response. They were not supportive of a hypothesis of an adverse association between dioxin and delays in development or hyperkinetic syndrome.

5.2.3.6. Multiple Birth Defects

Of 1,772 births after the father's service in SEA, 57 had multiple birth defects that could not be attributed to recognized syndromes. The rate of multiple birth defects in children of Ranch Hands with the highest categorized dioxin levels was not elevated. The data did not support an association between dioxin and multiple birth defects

5.2.3.7. Neural Tube Defects

Among 792 live-born infants to Ranch Hand fathers and 981 live-born infants to Comparison fathers, four children from Ranch Hand fathers and zero children from Comparison fathers had spina bifida or anencephaly, which are both neural tube defects.

5.2.3.8. Neonatal Deaths

Among children born after the Ranch Hand father's service in SEA, the rate of neonatal deaths (childhood death within 28 days of birth) was higher in children of Ranch Hands with the highest categorized dioxin levels than in children of Comparisons. Corresponding data, however, showed the same pattern among children born before the Ranch Hand father's service in SEA. Therefore, the findings appeared to be due to chance rather than to paternal dioxin exposure.

5.3. ARTICLES

5.3.1. Paternal Serum Dioxin and Reproductive Outcomes among Veterans of Operation Ranch Hand

This article (2) considered conceptions and children of Ranch Hands and Comparisons who were conceived during or after the father's service in SEA and whose father attended the 1987 physical examination and had a dioxin level (<10ppt for Comparisons). All analyses were adjusted, via stratification, for five covariates; father's race, mother's smoking during pregnancy, mother's drinking during pregnancy, father's age at time of child's birth, and father's military occupation. Spontaneous abortion was also adjusted for the occurrence of spontaneous abortion before father's service in SEA.

Few associations were found between dioxin and semen abnormalities, inability to conceive prematurity, neonatal deaths, birth defects, birth defect severity, and developmental abnormalities. Associations were generally weak, inconsistent, or biologically implausible. There was no meaningful elevation in spontaneous abortion or stillbirth.

There were some elevations in risk in some birth defect organ system categories, which, after review of the clinical descriptions, were not considered biologically meaningful. An increase in nervous system defects in children of Ranch Hand with increased paternal dioxin was observed, but it was based on sparse data. There was no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin.

5.3.2. Paternal Dioxin, Preterm Birth, Intrauterine Growth Retardation, and Infant Death

This article (3) studied dioxin body burden and preterm birth, intrauterine growth retardation (IUGR) and infant death of offspring born during or after father's SEA service of AFHS participants who attended either 1982, 1985, 1987 or 1992 physical examinations and had a dioxin level. All analyses were adjusted, via stratification, for six covariates; father's race, mother's smoking during pregnancy, mother's drinking during pregnancy, mother's age at time of child's birth, father's age at time of child's birth, and father's military occupation. Also, analyses were done excluding children whose mother had hypertension complicating pregnancy, childbirth, and puerperium; antepartum hemorrhage, abrupto placentae, and placenta previa; Rh incompatibility; infection of the amniotic cavity; secondary uterine inertia; or obesity. There was no association between paternal dioxin level and IUGR. The risk of preterm birth and infant death was increased among Ranch Hand children whose fathers had the highest dioxin levels and among children whose fathers had background dioxin levels. This pattern implied that these outcomes may not be related to paternal dioxin level.

5.3.3. Letter to the Editor: Paternal Dioxin and the Sex of Children Fathered by Veterans of Operation Ranch Hand

A study of people exposed to dioxin after an industrial accident in Seveso, Italy, found an excess of female offspring in families where both parents were highly exposed to dioxin. From 9 months after the accident, on July 10, 1976, to December 1984, the nine mother-father pairs with the highest dioxin levels had 12 children, all of which were girls.

AFHS researchers conducted a similar analysis and found no suggestion of a relation between paternal dioxin level and the sex of offspring (6). These findings suggested that, if the excess of female offspring seen in the Seveso study was male-mediated, the Ranch Hand exposure was not sufficient to produce the effect, or the effect was not male-mediated. The AFHS did not measure serum dioxin concentrations in the wives and partners of these veterans and their occupational exposures to dioxin or other chemicals were not known; however, that as a group it was thought they had experienced only background exposure.

5.4. CONCLUSION

The lack of an association between dioxin and total conceptions and between dioxin and any examined semen characteristics did not support the idea that dioxin was adversely related to the ability to father children. Dioxin also was unrelated to miscarriage, total adverse outcomes, birth weight, all 13 categories of birth defects, and neonatal death, and thus did not support the possibility of an adverse relation between dioxin and reproductive outcomes. The few positive associations that were found between dioxin and reproductive outcomes were generally weak, inconsistent, or biologically implausible.

Four children from Ranch Hand fathers and zero children from Comparison fathers had neural tube defects (spina bifida or ancephaly). This result, along with the two other epidemiological studies, led the IOM Committee to conclude that there was "limited/suggestive" evidence of an association between exposure to herbicides and spina bifida in the offspring of exposed individuals (7).

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6. MORTALITY

6.1. INTRODUCTION

The AFHS protocol specified that the mortality of Ranch Hand and Comparison subjects be examined across the 20-year period of the Study. The USAF Military Personnel Center records, the Veterans Administration Death Beneficiary Identification and Record Location System, and the Internal Revenue Service database of active social security account numbers were used to determine the subjects' deaths. Death certificates were ordered from the vital statistics department of the appropriate state or foreign country. The underlying cause of death was classified according to National Center for Health Statistics decision tables. Deaths from the date of the start of the veteran's duty in SEA were included, except for veterans killed in action during the Vietnam War. These veterans were excluded from the analysis because the immediate effects of herbicide exposure were not thought to have caused Ranch Hand combat deaths.

The AFHS protocol specified that up to 10 Comparisons were to be matched to each Ranch Hand according to date of birth, rank, race, and occupation, and that five Comparisons from each matched set were to be randomly chosen and used as the Comparison cohort for mortality studies. There were concerns that this randomly chosen Comparison cohort might not be representative of the mortality of all matched Comparisons. Data analyses performed prior to the 1989 Mortality Update (1) suggested that the mortality experience of the randomly chosen Comparison cohort was, purely by chance, not representative of the mortality experience of the entire matched Comparison cohort. After the concurrence of the Ranch Hand Advisory Committee appointed by the Agent Orange Working Group, the Comparison cohort was expanded to include all matched Comparisons after the 1986 Mortality Update (2) and prior to the 1989 Mortality Update (1). No differences in the conclusions were seen in the 1989 Mortality Update (1), regardless of whether the randomly selected Comparisons or the entire Comparison cohort were used.

The published reports or articles displayed in the table below concern mortality in the AFHS population. A brief summary of these reports follows.

Report or Article	Verified Deaths through	Deaths (Population Size)	
		Ranch Hand	Comparison
Baseline Mortality Study Results (30 June 1983)[1]	31 December 1982	50 (1,247)	250 (6,171)
Mortality Update – 1984 (10 December 1984)[2]	31 December 1983	54 (1,256)	265 (6,171)
Mortality Update – 1985 (29 November 1985)[3]	31 December 1984	55 (1,257)	285 (6,171)
Mortality Update – 1986 (26 December 1986)[4]	31 December 1985	59 (1,257)	312 (6,171)
Mortality Update – 1989 (17 April 1989)[5]	31 December 1987	74 (1,261)	376 (6,250)
[6]	31 December 1987	74 (1,261)	1,039 (19,101)
Health Status of Air Force Veterans Occupationally Exposed to Herbicides in Vietnam 2. Mortality (in *The Journal of the American Medical Association*)[7]	31 December 1987	74 (1,261)	1,038 (19,101)
Mortality Update – 1991 (15 October 1991)[8]	31 December 1989	91 (1,261)	1,241 (19,080)
Mortality Update – 1993 (October 1993)[9]	31 December 1991	106 (1,261)	1,439 (19,080)
Mortality Update – 1994 (13 September 1994)[10]	31 December 1992	111 (1,261)	1,545 (19,080)

Report or Article	Verified Deaths through	Deaths (Population Size)	
		Ranch Hand	Comparison
Mortality Update – 1996 (July 1996) [11]	31 December 1993	118 (1,261)	1,672 (19,080)
Postservice Mortality of U.S. Air Force Veterans Occupationally Exposed to Herbicides in Vietnam: 15-Year Follow-up (25 March 1998) (in *American Journal of Epidemiology*) [12]	31 December 1993	118 (1,261)	1,672 (19,080)
Post-service mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War (May 2005) (in *Military Medicine*) [13]	31 December 1999	186 (1,262)	2,330 (19,078)
Post-service mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War (June 2006) [14]	31 December 2003	240 (1,263)	2,734 (19,080)

[1] Comparison deaths based on a randomly chosen cohort of five matched Comparisons.

[2] Comparison deaths based on a randomly chosen cohort of five matched Comparisons. Added nine newly identified Ranch Hands (one died before 1983).

[3] Comparison deaths based on a randomly chosen cohort of five matched Comparisons. Added one newly identified Ranch Hand.

[4] Comparison deaths based on a randomly chosen cohort of five matched Comparisons.

[5] Comparison deaths based on a randomly chosen cohort of five matched Comparisons. Additions: 151 Comparisons were matched to 4 newly discovered Ranch Hands and 15 previously unmatched Ranch Hands.

[6] Comparison deaths based on entire Comparison population (10,133 matched and 8,958 unmatched. Additions are the same as [5].

[7] Comparison deaths included entire Comparison population. No additions or deletions

[8] Comparison deaths included entire Comparison population. 21 Comparisons were declared ineligible because SEA tour dates could not be confirmed due to missing service records. In addition, one Comparison was verified as ineligible and 11 veterans were newly verified as eligible Comparisons.

[9] Comparison deaths included entire Comparison population. No additions or deletions

[10] Comparison deaths included entire Comparison population. No additions or deletions

[11] Comparison deaths included entire Comparison population. No additions or deletions

[12] Comparison deaths included entire Comparison population. No additions or deletions

[13] Comparison deaths included entire Comparison population. One Comparison was determined to be a Ranch Hand and was moved to the Ranch Hand cohort; removed another Comparison who was determined to not belong to either group.

[14] Comparison deaths included entire Comparison population. Added one newly identified Ranch Hand and two newly identified Comparisons.

When analyses were restricted to participants attending a physical examination and had either an herbicide exposure index or 1987 dioxin levels then results were adjusted for potential risk factors such as drinking, smoking, and family history.

6.2. 1983 BASELINE MORTALITY STUDY

As reported in the 1983 Baseline Mortality Study Results report (6), 50 Ranch Hand and 250 Comparisons had died as of 31 December 1982. Analyses showed that the mortality experience of the Ranch Hand group was nearly identical to that of the Comparison group. The authors cautioned, however, that this mortality report could in no way be regarded as conclusively negative because the study population may not have reached the latency period in which attributable fatal disease might have been expected and detected. The cohort of deaths at that time was small, and both the Ranch Hand and Comparison groups were young and relatively healthy.

6.3. 1984 MORTALITY UPDATE

As of 31 December 1983, 54 Ranch Hands and 265 Comparisons had died. As described in the 1984 Mortality Update (7), no differences between Ranch Hand and Comparison mortality were found. Cause-specific analyses did not show any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy, circulatory system disease, or digestive system disease. No relation was found between mortality in Ranch Hands and the Air Force herbicide exposure index (described in Chapter 2). Continued mortality surveillance was recommended because the study groups were still relatively young and healthy.

6.4. 1985 MORTALITY UPDATE

As of 31 December 1984, 55 Ranch Hands and 285 Comparisons had died. The analyses described in the 1985 Mortality Update (8) found no differences between Ranch Hand and Comparison mortality. Cause-specific analyses did not show any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy, circulatory system disease, or digestive system disease. No relation was found between mortality in Ranch Hands and the herbicide exposure index. An interaction involving age and military occupation, however, was discovered in these analyses. Older Ranch Hand officers (older than 35 years of age) experienced fewer deaths than older Comparison officers, but younger Ranch Hand officers (35 years of age or younger) experienced more deaths than younger Comparison officers. Continued mortality surveillance was again recommended because the study groups were still relatively young and healthy.

6.5. 1986 MORTALITY UPDATE

As of 31 December 1985, 59 Ranch Hands and 312 Comparisons had died, as reported in the 1986 Mortality Update (2). The conclusions and recommendations remained unchanged from the 1985 Mortality Update.

6.6. 1989 MORTALITY UPDATE

The next AFHS Mortality Update was published in 1989 (1). A subsequent article in *The Journal of the American Medical Association* (3) also presented the results of this update. As of 31 December 1987, 74 Ranch Hands and 376 Comparisons had died, based on using the original Comparison cohort. For this update, the Comparison cohort was expanded to include the entire Comparison population (matched and unmatched) who flew or serviced C-130 cargo aircraft in SEA during the same calendar period that the Ranch Hand unit was active in Vietnam. This change in the Comparison cohort accounts for the marked increase in Comparisons deaths (1,039 Comparison deaths as of 31 December 1987).

As in previous updates, no differences between Ranch Hand and Comparison mortality were found in the 1989 Mortality Update (1). No difference between the observed and the expected number of deaths in Ranch Hands was seen when the cumulative mortality from all causes was examined. Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, homicide, malignancy, or circulatory disease. Digestive system deaths were more frequent in Ranch Hands than expected. Five of the six digestive system deaths, however, were attributable to alcohol consumption; the finding was considered unrelated to herbicide exposure. No relation was found between mortality in Ranch Hands and the herbicide exposure index.

6.7. 1991 MORTALITY UPDATE

As of 31 December 1989, 91 Ranch Hands and 1,241 Comparisons had died. The 1991 Mortality Update (9) was also the first report in which analysis of mortality in relation to serum dioxin levels was available (see Chapter 2). Prior to this report, the herbicide exposure index was used to assess dose-response trends within Ranch Hands.

An excess of deaths occurred from circulatory disease among Ranch Hand enlisted groundcrew personnel. The authors were concerned about this increase because Ranch Hand enlisted groundcrew had a higher median dioxin level than enlisted flyers or officers, and because dioxin levels were associated with diabetes and lipid abnormalities. Whereas there was no association between dioxin and cardiovascular disease in living Ranch Hands, it was considered possible that an increase in circulatory disease deaths could be dioxin-related through its association with diabetes and serum lipids.

Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, malignancy, or circulatory disease. The increase of digestive system deaths in Ranch Hands continued; nine Ranch Hands died from digestive diseases.

Because none of the 91 Ranch Hands who were deceased had been assayed for dioxin, the dioxin assay could not be used for this update to assess dose-response patterns in the mortality data. Analyses of mortality data in relation to dioxin levels were conducted for subsequent mortality updates.

6.8. 1993 MORTALITY UPDATE

As of 31 December 1991,106 Ranch Hands and 1,439 Comparisons were deceased. An evaluation of the cumulative Ranch Hand mortality from all causes through 31 December 1991 found no difference in the observed number of deaths from what was expected of a cohort of this size and age, as reported in the 1993 Mortality Update (10). An increasing trend occurred in death from all causes in Ranch Hand enlisted flyers during the 1989 to 1991 period. Of the seven Ranch Hand enlisted flyers who died during that period, five were due to a malignant neoplasm. This trend was not seen in Ranch Hand enlisted groundcrew, who were more heavily exposed to dioxin on average.

Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, homicide, and deaths due to infectious or parasitic diseases, deaths due to a malignant neoplasm, deaths due to endocrine disease, or deaths due to circulatory disease. The increase in digestive system deaths in Ranch Hands continued, as did the increase in deaths from circulatory disease among Ranch Hand enlisted groundcrew personnel.

For 872 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no difference in the average 1987 dioxin levels between 856 Ranch Hands who were still alive and the 16 Ranch Hands. No relation between survival time and dioxin levels existed.

6.9. 1994 MORTALITY UPDATE

As of 31 December 1992, 111 Ranch Hands and 1,545 Comparisons had died. As reported in the 1994 Mortality Update (11), no difference between the observed and the expected number of deaths in Ranch Hands was seen when the cumulative mortality from all causes was examined. Cause-specific analyses found no increase in overall Ranch Hand mortality from accidental deaths, suicides, homicides, deaths due to infectious and parasitic diseases, deaths due to malignant neoplasms, deaths due to endocrine disease, or deaths due to circulatory diseases. As with previous updates, the increase in digestive system deaths in Ranch Hands and deaths from circulatory disease among Ranch Hand enlisted groundcrew personnel was observed. A new finding on deaths due to ill-defined or unknown causes, however, was seen for the first time in this update. The number of deaths due to ill-defined or unknown causes increased among Ranch Hand enlisted flyers.

For 988 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no difference in the average 1987 dioxin levels between 968 Ranch Hands who were still alive and the 20 Ranch Hands. There also was no relation between survival time and 1987 dioxin levels.

6.10. 1996 MORTALITY UPDATE

As reported in the 1996 Mortality Update (12), 118 Ranch Hands and 1,672 Comparisons had died. No difference between the observed and the expected number of deaths in Ranch Hands was seen when the cumulative mortality from all causes through 31 December 1993 was examined. Cause-specific analyses found no increase in overall Ranch Hand mortality from accidental deaths, suicides, homicides, deaths due to infectious and parasitic diseases, deaths due to malignant neoplasms, deaths due to endocrine disease, deaths due to respiratory disease, deaths due to circulatory disease, or deaths due to ill-defined or unknown causes. An increase in deaths due to digestive disease was no longer seen, and an increase in deaths in Ranch Hand enlisted flyers due to ill-defined or unknown causes was no longer present. The increase in deaths due to digestive disease was no longer significant because no additional digestive disease deaths had been reported between 31 December 1992, the time of the previous report, and 31 December 1993. The number of expected deaths had increased, however, because of the additional year under study. The increase in the number of expected deaths decreased the standardized mortality ratio to a level that was not statistically significant. There were 30 deaths due to malignant neoplasms, but they did not appear to aggregate in an unusual pattern relative to what would have been expected. The increase in deaths from circulatory disease among Ranch Hand enlisted groundcrew that was reported since the 1991 Mortality Update (9) was still present, although no new circulatory disease deaths in this cohort were reported since the 1994 Mortality Update (11). Further analysis of circulatory disease deaths in enlisted groundcrew revealed that more than 65 percent of these deaths were due to atherosclerotic heart disease.

For 991 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no difference in the average 1987 dioxin levels between 968 Ranch Hands who were still alive and the 23 Ranch Hands. There also was no relation between survival time and 1987 dioxin levels.

Further analysis was performed and reported in a 1998 journal article (13) describing the mortality of AFHS veterans. In particular, in the subgroup of Ranch Hand veterans that had survived more than 20 years since their military service in SEA, no increase in the risk of death due to cancer at all sites was found.

6.11. 1999 MORTALITY UPDATE

As described in a journal article published in 2005 (14), as of 31 December 1999, 186 Ranch Hands and 2,330 Comparisons had died. The risk of death caused by cancer was not increased, but the risk of death

caused by circulatory system diseases was increased in enlisted groundcrew. When circulatory disease was divided into five categories—atherosclerotic heart disease, cardiomyopathy, cerebrovascular disease, hypertensive disease, and other circulatory diseases—the strongest association between group and circulatory system disease was because of atherosclerotic heart disease. The cumulative all-cause mortality experience of Ranch Hands was not statistically greater than Comparisons, but the authors thought this trend required further monitoring to confirm the increased risk suggested by these results.

To examine cancer mortality in a way that accounts for latency, the risk was evaluated among those subjects who survived at least 20 years after entry into follow-up. No differences were found in this subset, as was also the case with cancer mortality within 20 years of service in SEA.

6.12. 2006 MORTALITY UPDATE

As reported in the technical report published in 2006 (15), 240 Ranch Hands and 2,734 Comparisons had died as of 31 December 2003. For the first time, the cumulative all-cause mortality experience of Ranch Hands was significantly increased compared to the Comparisons. The risk of death caused by circulatory system diseases was not only increased in enlisted ground crew as previously seen but also for all occupations (officer, enlisted groundcrew, etc) combined. The risk of death caused by cancer was not increased.

All-cause mortality and mortality due to cancer and circulatory disease among AFHS veterans who attended at least one physical examination regardless of dioxin assay status were evaluated. After adjustment for risk factors, the risk of all-cause and cancer deaths were not increased. However, deaths caused by circulatory disease were increased, mainly due to elevated risk among enlisted ground crew. Similar results were found when analysis was restricted to AFHS veterans who had dioxin levels (1,027 Ranch Hands and 1,524 Comparisons); no increase in all-cause and cancer deaths but deaths due to circulatory disease were increased in the low category and in the high category.

To examine cancer mortality in a way that accounts for latency, the risk was evaluated among those subjects who survived at least 20 years after entry into follow-up. No differences were found in this subset, as was also the case with cancer mortality within 20 years of service in SEA.

6.13. CONCLUSION

Based on deaths through 31 December 2003, 240 Ranch Hands and 2,734 Comparisons had died. The risk of death attributable to circulatory system diseases, first observed to be significantly increased in Ranch Hands in the 1991 Mortality Update (deaths through 1989), continued to increase, especially for enlisted groundcrew, the subgroup with the highest dioxin levels. Similar significant elevations in the risk of circulatory disease death were seen among the subgroup of veterans who attended a physical examination. Among those veterans who attended an examination and who were assayed for dioxin, a significant increasing trend in the risk of death due to circulatory system disease was observed as dioxin levels increased.

Furthermore, all-cause mortality through 31 December 2003 found an increased risk of death in Ranch Hand veterans for the first time. However, there was no increase in risk of death from cancer. Also, since the 1996 mortality update the increase in deaths from digestive disease, as first identified in the 1989 mortality update, was no longer present.

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7. GENERAL HEALTH ASSESSMENT

7.1. INTRODUCTION

For the six physical examinations (1-7), four variables were included in the AFHS general health assessment: self-perception of health, appearance of illness or distress during the examination, relative age, and body mass index. For the evaluation of self-perception of health, each participant was asked to rate his health (excellent, good, fair, poor) compared to other people his age. In addition, a board-certified internist examined the participants for the appearance of acute illness or distress (yes or no). To determine relative age, the internist assessed whether each subject appeared younger than, older than, or the same as his stated age. Body mass index (BMI) [called body fat at the 1982 baseline examination] was computed based on height and weight recorded at the physical examinations.

The BMI is an approximate measurement of the percentage of a person's body mass that can be attributed to fat. The BMI serves as a valuable clinical clue to the likelihood of disease and helps define obesity-an important health risk factor.

The following chart lists the variables that were analyzed for the general health assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Appearance of Illness or Distress	X	X	X	X	X	X	X
Body Mass Index/Body Fat	X	X	X	**X**	**X**	**X**	**X**
Relative Age Appearance as Assessed by a Physician	**X**	X	X	X	**X**	X	X
Self-perception of Health	**X**	**X**	X	**X**	**X**	**X**	X

7.2. BODY MASS INDEX

Beginning with the dioxin measurements in 1987, analyses showed increased body fat with increasing dioxin within Ranch Hands. This relation was evident for initial dioxin, categorized dioxin, and 1987 dioxin. The same patterns with dioxin, particularly categorized dioxin and 1987 dioxin, were observed for the analyses of the 1992, 1997, and 2002 follow-up examination data.

When the body fat measure or body mass index was categorized as obese (body mass index greater than 30 for the 2002 follow-up examination) or normal (less than 30), the same patterns were seen. Beginning with the dioxin measurements in 1987, analyses showed increasing obesity with dioxin within Ranch Hands. Similar patterns with dioxin, particularly categorized dioxin and 1987 dioxin, were observed for the analyses of the 1992, 1997, and 2002 follow-up examination data. The percentage of obese participants, however, was similar between Ranch Hands and Comparisons.

The association appeared to be due to slower dioxin elimination pharmacokinetics in obese participants relative to participants who were lean or not obese (8). In part, participants with the highest dioxin levels retained dioxin due to their higher body fat content.

7.3. SELF-PERCEPTION OF HEALTH

During the health interview administered for all examinations, each AFHS participant was asked the following: "Compared to other people your age, would you say your health is excellent, good, fair, or poor?" This self-reported perception was analyzed as a measure of the general health status of each participant, although it was recognized that the perception was susceptible to varying degrees of conscious and subconscious bias (e.g., in 1992 and after, most participants were aware of their serum dioxin levels). This variable was dichotomized as excellent and good, and fair and poor for analyses.

At the 1982 baseline examination, more Ranch Hands perceived their health to be fair or poor than Comparisons. This pattern was seen at the 1985, 1992, and 1997 follow-up examinations, with the largest difference among enlisted groundcrew. Differences between Ranch Hands and Comparisons were not observed at the 2002 follow-up examination.

Similar patterns were observed when examining the relation between self-perception of health and measures of dioxin. In 1987, 1992, and 1997, the percentage of participants perceiving their health as fair or poor increased with increased dioxin levels. An association between self-perception of health and measures of dioxin, however, was not observed at the 2002 follow-up examination.

7.4. CONCLUSION

Self-perception of health has shown mixed results since 1982. More Ranch Hands perceived their health to be fair or poor than Comparisons in 1982, 1985, 1992, and 1997 follow-up examinations. However, in 1987 and 2002 studies, no appreciable differences were seen between Ranch Hand and Comparisons. In 1987, 1992, and 1997 the percentage of participants perceiving their health as fair and poor increased with increased dioxin levels. However, this was not seen in 2002. Thus, no persistent or emergent impact of herbicide or dioxin exposure on this general health measure was observed.

BMI was positively associated with categorized and 1987 dioxin in all the examinations since 1987. Obesity was highly correlated with dioxin levels. This probably reflected the pharmokinetics of dioxin elimination.

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8. CARDIOVASCULAR ASSESSMENT

8.1. INTRODUCTION

Cardiac disease and peripheral vascular disease are not recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin. Both bradycardia and tachycardia have been suggested following acute heavy exposures to the 2,4-D and 2,4,5-T components, but the cardiovascular effects after chronic low-dose exposure are essentially unknown. To assess cardiovascular function and exposure to herbicides, the AFHS collected data by questionnaire and physical examination to identify a number of cardiac endpoints.

Analyses were performed to assess the cardiovascular function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). The cardiovascular analyses were based on medical records verification of the data collected from questionnaires and physical examination findings.

The questionnaire captured data on the occurrence of heart conditions and the medical records review confirmed these reported conditions and identified any unreported conditions for each participant. As a result, a history of essential hypertension, heart disease (excluding essential hypertension), myocardial infarction and stroke or transient ischemic attack was determined for each participant.

The physical examination assessed the cardiac function by measurements of systolic blood pressure, diastolic blood pressure, heart sounds (by auscultation), and an electrocardiograph (ECG). The standard 12-lead ECG was performed and rhythm strips were obtained for all participants. The ECG findings were analyzed at each of the six physical examinations. The following components of the ECG have been analyzed since the 1985 follow-up examination: right bundle branch block (RBBB), left bundle branch block (LBBB), nonspecific ST- and T-wave changes, bradycardia (a resting pulse rate less than 50 beats per minute), tachycardia (a resting pulse rate greater than 100 beats per minute), arrhythmia, evidence of a prior myocardial infarction, and other diagnoses (ventricular aneurysm and Wolff-Parkinson-White syndrome).

The peripheral vascular function was assessed by funduscopic examination of small vessels of the eyes, the presence or absence of carotid bruits, and the examination of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. In 1982, 1985, and 1987, manual techniques were used to examine peripheral pulses. In 1985, the Doppler technique also was introduced to make these measurements and replaced the manual method for the 1992 through 2002 examinations.

The Doppler procedure for examining pulses involved a set of measurements designed to determine whether a pulse abnormality existed, where the obstruction was most likely located, and whether it had functional implications. Pulses were considered abnormal if no arterial flow or a monophasic arterial flow was present on either side.

In addition, two pulse indices were constructed from the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulse measurements, as follows:

- Peripheral pulses: radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses
- Leg pulses: femoral, popliteal, dorsalis pedis, and posterior tibial pulses.

For the 1982, 1985, and 1987 physical examinations, the assessment of all pulses (carotid pulse and peripheral pulses) was analyzed. Each of these indices was considered normal if all pulses were normal, and abnormal if one or more pulses were abnormal.

At the 1987 follow-up examination an increase in abnormal peripheral pulses in Ranch Hands was observed so, at the 1992 follow-up examination kidney, ureter, bladder (KUB) x-rays were used to detect hardening of the arteries and to screen for vascular disease. If no such abnormalities were present or the only abnormality was the presence of kidney stones, then the KUB x-ray was defined as normal. Kidney stones, as diagnosed from the KUB x-ray, were examined separately in the Renal Assessment.

Assessment of peripheral vascular function included several analyses. In 1992, the results of KUB x-ray findings and participant responses to the supplemental questionnaire, "Pain in Legs", were analyzed. In 2002, a resting blood pressure index and two hyperemic indices were used as measures of intermittent claudication.

The following questions from the 1992, 1997, and 2002 supplemental questionnaire were used as a self-reported assessment of claudication and vascular insufficiency:

- Do you get a pain in either or both of your legs while walking?
- Does this pain ever begin when you are standing still or sitting?
- Do you get this pain in either or both of your calf muscles?

An intermittent claudication and vascular insufficiency index was based on the responses to the above questions. The answers were used to detect intermittent claudication and vascular insufficiency (yes, no), which indicate an insufficient oxygen supply to the leg muscles. A participant was judged to have intermittent claudication and vascular insufficiency if he answered "yes" to the first and third questions and "no" to the second question.

Three indices of claudication using peripheral blood pressure measurements were analyzed at the 2002 follow-up examination. Right and left brachial (upper arm) blood pressures were taken during the vascular examination using the Doppler technique. After brachial pressures were recorded, the right and left supine ankle pressures were measured. A resting pressure index was calculated from the resting ankle systolic pressure and the brachial systolic pressure. Post-exercise pressures were obtained at the ankle and the brachial arteries at the site of the highest pressures before exercise. Brachial and ankle pressures were obtained at 1 minute post-exercise and 2 minutes post-exercise, and two hyperemic pressure indices of claudication were calculated from these measurements after exercise.

AFHS staff and colleagues published the following articles:

- Post-service Mortality of Air Force Veterans Occupational Exposed to Herbicides during the Vietnam War (8)
- Hypertension and 2,3,4,8-tetrachlorodibenzo-p-dioxin in Air Force Veterans of the Vietnam War (9).

The first IOM *Veterans and Agent Orange* report in 1994 (10) concluded that there was "inadequate or insufficient" evidence to establish an association between dioxin exposure and the occurrence of specific circulatory disorders, including coronary artery disease, myocardial infarction, stroke and hypertension, or circulatory diseases in general. The findings remained unchanged in all subsequent *Veterans and Agent Orange* updates (11-15).

The following chart lists the cardiovascular variables that were analyzed and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Blood Pressure: Diastolic	X	X	**X**	**X**	**X**	X	**X**
Blood Pressure: Systolic	X	X	X	**X**	X	X	X
Carotid Bruits	X	X	X	X	**X**	X	X
ECG: Arrhythmia		X	X	**X**	**X**	X	X
ECG: Bradycardia		X	X	X	**X**	X	X
ECG: Evidence of Prior Myocardial Infarction					**X**	**X**	X
ECG: LBBB		X	X	X	X	X	X
ECG: Nonspecific ST- and T-wave Changes		X	X	X	**X**	X	X
ECG: Other Diagnoses		X	X	**X**	**X**	**X**	X
ECG: Overall	X	X	X	X	**X**	X	X
ECG: RBBB		X	X	X	**X**	X	X
ECG: Tachycardia		X	X	X	X	**X**	X
Essential Hypertension		X	X	X	**X**	**X**	X
Funduscopic Examination	X	X	X	X	**X**	X	X
Heart Disease (Excluding Essential Hypertension)	X	**X**	X	X	X	**X**	**X**
Heart Sounds	X	X	X	X	X	X	X
Intermittent Claudication and Vascular Insufficiency Index					X	X	X
Myocardial Infarction		X	X	**X**	**X**	X	X
KUB X-ray (excluding kidney stones)					**X**		
Pressure Index: Hyperemic (1 minute post-exercise)							X
Pressure Index: Hyperemic (2 minutes post-exercise)							X
Pressure Index: Resting							X
Pulses: All	X	X	X	**X**			
Pulses: Dorsalis Pedis	X	X	X	**X**	**X**	X	X
Pulses: Femoral	X	X	**X**	**X**	**X**	X	X
Pulses: Leg	X	X	X	**X**	**X**	X	X
Pulses: Peripheral	**X**	X	X	**X**	**X**	X	X
Pulses: Popliteal	X	X	X	X	**X**	X	X
Pulses: Posterior Tibial	X	**X**	X	**X**	**X**	X	X
Pulses: Radial	X	X	X	X	X	X	X
Stroke or Transient Ischemic Attack						X	X

8.2. BLOOD PRESSURE

8.2.1. Diastolic

Among the younger participants, Ranch Hands had a higher average diastolic blood pressure than Comparisons at the 1987 follow-up examination. Among participants with type B personalities, diastolic blood pressure values increased with increasing initial dioxin levels. Among participants with type B personalities and a family history of heart disease, Ranch Hands in the low dioxin category had a higher average diastolic blood pressure than Comparisons. In addition, among participants with type B

personalities and no family histories of heart disease, Ranch Hands in the high dioxin category had a greater average diastolic blood pressure than Comparisons.

Among officers, diastolic blood pressure values at the 1992 follow-up examination increased as initial dioxin levels increased.

Analysis of 2002 follow-up examination data showed that Ranch Hands in the high dioxin category had a greater percentage of participants with abnormal diastolic blood pressure readings (>90 mm Hg) than Comparisons.

8.2.2. Systolic

At the 1992 follow-up examination among participants with type B personalities who had later tours of duty, the percentage of participants with abnormally high systolic blood pressure values (>140 mm Hg) increased with increasing 1987 dioxin levels. In addition, the analysis showed that among younger participants, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high systolic blood pressure values than Comparisons.

8.3. CAROTID BRUITS

Among the heaviest drinkers throughout their lifetimes in the 1992 follow-up examination (greater than 40 drink-years), Ranch Hands in the background and high dioxin categories had a greater prevalence of carotid bruits than Comparisons.

8.4. ECG

8.4.1. Arrhythmia

For participants with later tours of duty, the occurrence of arrhythmias increased as 1987 dioxin levels increased at the 1992 follow-up examination. The prevalence of arrhythmia increased with increasing initial dioxin levels for participants with type A personalities.

Among participants who had never smoked, the percentage of Ranch Hands at the 1992 follow-up examination with arrhythmias increased with increasing levels of initial dioxin and 1987 dioxin. Among participants with low high-density lipoprotein (HDL) cholesterol levels ($\leq$35 mg/dL), Ranch Hands in the high dioxin category had a greater prevalence of arrhythmias than Comparisons.

8.4.2. Bradycardia

Ranch Hand enlisted flyers at the 1992 follow-up examination had a greater occurrence of bradycardia than Comparison enlisted flyers. Ranch Hands in the background dioxin category had a greater prevalence of bradycardia than Comparisons, primarily among participants with type B personalities.

8.4.3. Evidence of Prior Myocardial Infarction

Among nondiabetic Ranch Hands, the percentage of participants with evidence of a prior myocardial infarction at the 1992 follow-up examination, as determined from the ECG, increased with increasing initial dioxin. In addition, evidence of prior myocardial infarction in Ranch Hands increased with increasing 1987 dioxin levels.

The percentage of Ranch Hands at the 1997 follow-up examination with evidence of a prior myocardial infarction increased with increasing initial dioxin levels.

8.4.4. Nonspecific ST- and T-Wave Changes

Based on data collected for the 1992 follow-up examination the presence of nonspecific ST- and T-wave changes increased with increasing 1987 dioxin levels.

8.4.5. Other Diagnoses

Analyses for the 1987 and 1997 follow-up examinations showed Ranch Hands in the high dioxin category had a greater occurrence of other ECG diagnoses than Comparisons.

Among Ranch Hand enlisted flyers, the prevalence of other ECG diagnoses at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

8.4.6. Overall

Among participants with normal cholesterol levels ($\leq$ 200 mg/dL) at the 1992 follow-up examination, the percentage of Ranch Hands with abnormal overall ECG results increased with increasing levels of initial dioxin, as well as with increasing levels of 1987 dioxin.

8.4.7. Right Bundle Branch Block (RBBB)

Among moderate lifetime smokers (no more than 10 pack-years), the prevalence of RBBB at the 1992 follow-up examination increased with increasing initial dioxin. Analysis of 1992 follow-up examination data also found that the percentage of Ranch Hands with RBBB increased with increasing 1987 dioxin levels.

8.4.8. Tachycardia

Ranch Hands in the high dioxin category had a greater prevalence of tachycardia than Comparisons at the 1997 follow-up examination.

8.5. ESSENTIAL HYPERTENSION

The prevalence of essential hypertension after service in SEA increased as 1987 dioxin levels increased based on data collected at the 1992 follow-up examination and again on data collected at the 1997 follow-up examination.

8.6. FUNDUSCOPIC EXAMINATION

The 1992 follow-up examination analysis showed that the percentage of Ranch Hands with an abnormal funduscopic examination increased with increasing 1987 dioxin levels.

8.7. HEART DISEASE (EXCLUDING ESSENTIAL HYPERTENSION)

The prevalence of heart disease after service in SEA was increased in Ranch Hands based on data at the 1985 follow-up examination.

The prevalence of heart disease after service in SEA, based on data collected at the 1997 follow-up examination, was increased in Ranch Hands and, in particular, in Ranch Hand enlisted flyers. In addition, Ranch Hands in the background dioxin category had a greater prevalence of heart disease than Comparisons.

Ranch Hand enlisted flyers had a greater prevalence of heart disease after service in SEA than Comparison enlisted flyers, based on data collected at the 2002 follow-up examination.

8.8. MYOCARDIAL INFARCTION

Among participants with a low differential cortisol response, Ranch Hands in the low dioxin category had a greater prevalence of myocardial infarction after service in SEA than Comparisons, based on data collected at the 1987 follow-up examination.

The analysis of myocardial infarction after service in SEA, based on data collected at the 1992 follow-up examination, found that among nonobese (approximate body mass index less than 30) participants, Ranch Hands in the high dioxin category had a greater prevalence of myocardial infarction than Comparisons.

8.9. KUB X-RAY (EXCLUDING KIDNEY STONES)

Among non-Black participants, the percentage of Ranch Hands with KUB x-ray abnormalities at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

8.10. PULSES

8.10.1. All Pulses

When examining all pulses collectively, analysis of data from the 1987 follow-up examination revealed interactions between initial dioxin and age, as well as between 1987 dioxin and lifetime smoking history. The percentage of Ranch Hand pulse abnormalities increased with increasing initial dioxin, primarily among older participants. Among Ranch Hands who were the heaviest lifetime smokers (greater than 10 pack-years) with later tours of duty, the prevalence of pulse abnormalities increased with increasing 1987 dioxin. A greater percentage of pulse abnormalities was seen among Ranch Hands in the low dioxin and high dioxin categories than among Comparisons.

8.10.2. Dorsalis Pedis Pulses

Analysis of 1987 follow-up examination data showed that the prevalence of dorsalis pedis pulse abnormalities increased with increasing 1987 dioxin among Ranch Hands with later tours of duty. The prevalence of dorsalis pedis pulse abnormalities increased as initial dioxin levels increased.

Among older participants and diabetic participants at the 1992 follow-up examination, Ranch Hands in the high dioxin category had a greater prevalence of dorsalis pedis pulse abnormalities than Comparisons.

8.10.3. Femoral Pulses

Analysis of data from the 1987 follow-up examination showed that a greater percentage of Ranch Hands and Ranch Hands in the high dioxin category had abnormal femoral pulses than Comparisons. In addition, among participants with type A personalities, the prevalence of femoral pulse abnormalities increased with increasing initial dioxin levels.

Ranch Hands in the low dioxin category had a greater prevalence of abnormal femoral pulses than Comparisons at the 1992 follow-up examination.

8.10.4. Leg Pulses

Leg pulses (peripheral pulses, with the exception of the radial pulses) at the 1987 follow-up examination mirrored the analysis of all pulses and peripheral pulses. Interactions between initial dioxin and age, as well as between 1987 dioxin and lifetime smoking history, were found. Also, a greater percentage of leg pulse abnormalities was seen among Ranch Hands in the low dioxin category and Ranch Hands in the high dioxin category than among Comparisons.

At the 1992 follow-up examination, analysis showed the prevalence of abnormal leg pulses in diabetic Ranch Hands in the high dioxin category was greater than diabetic Comparisons.

8.10.5. Peripheral Pulses

Ranch Hands at the 1982 baseline examination had a greater percentage of abnormal peripheral pulses than Comparisons. When examining peripheral pulses collectively, analysis of data from the 1987 follow-up examination revealed interactions between initial dioxin and age, as well as between 1987 dioxin and lifetime smoking history. The percentage of Ranch Hand pulse abnormalities increased with increasing initial dioxin, primarily among older participants. Among Ranch Hands who were the heaviest lifetime smokers (greater than 10 pack-years) with later tours of duty, the prevalence of peripheral pulse abnormalities increased with increasing 1987 dioxin. A greater percentage of pulse abnormalities was seen among Ranch Hands in the low dioxin and high dioxin categories than among Comparisons.

Analysis of diabetics at the 1992 follow-up examination showed that the percentage of diabetic Ranch Hands with abnormal peripheral pulses increased with increasing 1987 dioxin levels among Ranch Hands with no family history of heart disease. In addition, a higher percentage of Ranch Hand diabetics in the high dioxin category than Comparisons had abnormal peripheral pulses.

8.10.6. Popliteal Pulses

A greater percentage of Ranch Hands and Ranch Hands in the high dioxin category than Comparisons had abnormal popliteal pulses at the 1992 follow-up examination. In addition, among officers, the prevalence of popliteal pulse abnormalities increased with increasing 1987 dioxin levels.

8.10.7. Posterior Tibial Pulses

Ranch Hands had a greater percentage of posterior tibial pulse abnormalities than Comparisons at the 1985 follow-up examination, as measured by manual palpation.

The 1987 follow-up examination analysis found that Ranch Hands in the low dioxin category had a higher prevalence of abnormal posterior tibial pulses than Comparisons.

A greater percentage of Ranch Hands in the high dioxin category had posterior tibial pulse abnormalities than Comparisons at the 1992 follow-up examination. In addition, among moderate current cigarette smokers (no more than 20 cigarettes per day, on average), Ranch Hands in each of the dioxin categories (background, low, and high) had a greater percentage of posterior tibial pulse abnormalities at the 1992 follow-up examination than Comparisons.

8.11. ARTICLE AND TECHNICAL REPORT

8.11.1. AFHS Cardiovascular Mortality through 2003

As described in a 2006 technical report "Post-service Mortality of Air Force Veterans Occupationally Exposed to Herbicides during the Vietnam War" (8), as of 31 December 2003, 240 Ranch Hands and 2,734 Comparisons had died. These deaths were based on the 1,262 Ranch Hand and 19,080 Comparison veterans studied. The mortality rates were adjusted for year of birth and military occupation; no adjustment for race was performed because of the small number of Black veterans in the population. The risk of death caused by circulatory system diseases was not only increased in enlisted ground crew as previously seen but also for all occupations combined. Mortality due to circulatory diseases among AFHS veterans who attended at least one physical examination, regardless of dioxin assay status was evaluated. After adjustment for risk factors (smoking, drinking and family history),

deaths caused by circulatory disease were increased, mainly due to elevated risk among enlisted ground crew. Similar results were found when analysis was restricted to AFHS veterans who had dioxin levels (1027 Ranch Hands and 1524 Comparisons); deaths were increased in the low and high dioxin categories for deaths due to circulatory disease.

8.11.2. Hypertension and 2,3,7,8-tetrachlorodibenzo-p-dioxin in Air Force Veterans of the Vietnam War

An analysis based on veterans who had dioxin serum levels measured at the 1987, 1992, or 1997 follow-up examinations was conducted to investigate the risk of diagnosed hypertension and exposure to dioxin (9). There was no overall increase in the risk of hypertension in the Ranch Hand cohort, however, within both cohorts (Ranch Hand and Comparison) the risk of hypertension was markedly increased with dioxin. Relative to the bottom category of serum dioxin in the Comparison cohort, the relative risk of hypertension in the highest dioxin category in the Comparison group was 1.66 and 1.33 in the highest dioxin category in the Ranch Hand. Thus, the risk of hypertension increased with dioxin in both Ranch Hands and Comparisons and, without regard to dioxin, the risk was not increased in the Ranch Hand cohort, a phenomenon known as Simpson's Paradox. Simpson's Paradox has been described as an artifact of confounding. An analysis of a questionnaire-based index of skin exposure to herbicides among Ranch Hand enlisted personnel revealed an increasing trend of hypertension risk with increasing skin exposure. While the lack of an overall between-group difference in hypertension risk suggested that dioxin was not a risk factor for hypertension, these within-group associations suggested that mechanisms relating dioxin uptake and clearance were associated with body weight and the pathophysiology of hypertension.

8.12. CONCLUSION

The cardiovascular morbidity analyses of the six examinations, adjusted for all known risk and demographic factors, showed no consistent findings across the different dioxin measurement groups or the Ranch Hand and Comparison groups over the years. Many of the findings were only in subpopulations analyses. The technical report on hypertension and dioxin after adjustment for risk factors, stratification by dioxin level and the replacement of dioxin by reported skin exposure to herbicides showed a consistent pattern of increased risk in each cohort, but did not reveal a significant difference in risk between cohorts without regard to dioxin exposure. This suggested that dioxin was not a risk factor for hypertension but that metabolic processes involved in dioxin uptake and clearance may be linked to the pathophysiology of hypertension and change in body weight. However, the latest mortality study continued to show the previously seen increased risk of death due to circulatory causes. Although not adjusted for risk factors, the mortality study through 2003 showed the risk of death caused by circulatory system diseases was not only increased in enlisted ground crew as previously seen but also for all occupations combined. Mortality due to circulatory diseases among AFHS veterans who attended at least one physical examination, regardless of dioxin assay status was evaluated. After adjustment for some risk factors (smoking, drinking and family history), deaths due to circulatory disease were still increased, mainly due to elevated risk among enlisted ground crew. Similar results were found when analysis was restricted to AFHS veterans who had dioxin levels (1027 Ranch Hands and 1524 Comparisons); deaths were increased in the low and high categories for deaths due to circulatory disease. Thus, although there appeared to be an increase in circulatory deaths in Ranch Hands related to dioxin, morbidity data did not show a consistent relation with dioxin.

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9. DERMATOLOGY ASSESSMENT

9.1. INTRODUCTION

The dermatology assessment of participants in the AFHS included the occurrence of self-reported acne and dermatology examinations at the 1982, 1985, 1987, 1992, and 2002 examinations (1-6). Of particular interest at the initiation of the study was the detection of chloracne.

Chloracne is a skin condition recognized as a consequence of exposure to high levels of dioxin and other cyclic organochlorine compounds. It usually appears without long latency after a short interval of exposure to dioxin and persists for about 2 to 3 years after exposure has been discontinued. Chloracne lesions are typically found on the temples, eyes or ears. Chloracne might be suggested if secondary lesions, such as scarring, hyperpigmentation, and depigmentation, were observed in these areas.

Because of the short duration of chloracne after exposure, primary lesions were not expected to be noted at the AFHS physical examinations. No biopsies to confirm the diagnosis of chloracne were deemed necessary by the examining dermatologists. Analysis, therefore, was limited to secondary lesions, such as scarring, hyperpigmentation, and depigmentation. The occurrence, duration, and location of acne were studied because of the absence of chloracne in AFHS veterans and were the only objective way to assess for potential cases of chloracne.

During the questionnaire segment of the physical examination, each study participant was asked about occurrences of acne on the face. For follow-up examinations this information was used to update data gathered from previous examinations. Information regarding the date and location of each acne occurrence also was collected.

The analysis of acne was based on participant-reported occurrences rather than data from medical records verification because it was expected the majority of participants who reported acne did not visit a physician for the condition. Questions regarding the presence of acne included acne on the temples, eyes, or ears, as acne at these locations may have been related to chloracne. Total duration of acne was determined by adding the duration of each reported occurrence of acne from all AFHS questionnaires. A review of medical records did not find any documented cases of chloracne among AFHS participants.

A dermatology index was created by combining results for comedones, acneiform lesions, acneiform scars, and inclusion cysts. The index was defined as abnormal if any of these conditions was present and defined as normal if none was present.

An endpoint named "other abnormalities," was created for the 1982, 1985, 1987, and 1992 follow-up examinations. This endpoint included vitiligo, jaundice, spider angiomata, palmar erythema, palmar keratosis, actinic keratosis, petechia, ecchymosis, conjunctival abnormality, oral mucosal abnormality, fingernail abnormality, toenail abnormality, dermatographia, cutis rhomboidalis, nevus, and other nonspecific abnormalities. This variable was considered abnormal if at least one of the above conditions was present, and normal if all of the conditions were absent.

When the dermatologists discovered suspicious neoplasms at the physical examinations, contingent upon participant authorization, these lesions were biopsied and the pathology determined. Abnormalities relating to skin malignancies are discussed in Chapter 14, Neoplasia Assessment.

AFHS staff and colleagues wrote the following article:

- Serum dioxin, chloracne, and acne in veterans of Operation Ranch Hand (7).

In the 1994 *Veterans and Agent Orange* report published by the IOM, the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there was sufficient evidence of an association between exposure to dioxin and chloracne (8). This conclusion remained unaltered in the 2002 and 2004 IOM *Veterans and Agent Orange* updates (9, 10); however, the Committee added a notation that chloracne would appear shortly after dioxin exposure and not after a long latency (9).

The following chart lists the variables analyzed for the dermatology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Acne, Location (Post-Southeast Asia, excluding participants with pre-Southeast Asia acne)		X	X	X	X	Analysis not performed	
Acne (self-reported), Occurrence and Duration)	X	X	X	X	X		**X**
Acneiform Lesions	X	X	X	X			**X**
Acneiform Scars	X	X	X	**X**			X
Comedones	X	X	X	X			X
Depigmentation		X	X	X			X
Dermatologic Evaluation Abnormality: Any	X						
Dermatologic Evaluation: Other Abnormality	X	X	X	X	**X**		
Dermatology Index	X	X	X	X	**X**		X
Hyperpigmentation	X	X	X	**X**			X
Inclusion Cysts	X	X	X	X			X

9.2. ACNE (SELF-REPORTED), OCCURRENCE AND DURATION

The occurrence, location, and duration of acne were reported by the participants at each physical examination and combined to construct a lifetime history of acne. Based on the compilation of all examinations, the analyses performed for the 2002 follow-up examination showed that the occurrence of reported acne after service in SEA increased in Ranch Hand enlisted groundcrew, the subgroup with the highest median dioxin levels. The occurrence and duration of reported acne since SEA service increased in the background, low, and high Ranch Hand dioxin categories. In examining whether the occurrence of acne prior to service in SEA had an effect, it was discovered that the associations with dioxin were found only in participants who did not report acne prior to service in SEA.

9.3. ACNEIFORM LESIONS

The prevalence of acneiform lesions at the 2002 follow-up examination was greater for Ranch Hands in the background dioxin category than for Comparisons.

9.4. ACNEIFORM SCARS

As 1987 dioxin levels increased in Ranch Hands with later tours of duty, the occurrence of acneiform scars at the 1987 follow-up examination increased.

9.5. DERMATOLOGIC EVALUATION OF OTHER ABNORMALITIES

For participants who reported acne prior to their tour of duty in SEA, the percentage of participants who had these other abnormalities increased as initial dioxin increased at the 1992 follow-up examination.

9.6. DERMATOLOGY INDEX

Younger Ranch Hands in the background dioxin category had an abnormal dermatology index more often than younger Comparisons in the analysis of data collected at the 1992 follow-up examination.

9.7. HYPERPIGMENTATION

Among older participants, the prevalence of hyperpigmentation at the 1987 follow-up examination increased as initial dioxin levels increased. In addition, as 1987 dioxin levels increased in Ranch Hands with later tours of duty, the occurrence of hyperpigmentation at the 1987 follow-up examination increased.

9.8. ARTICLE

9.8.1. Serum Dioxin, Chloracne, and Acne in Veterans of Operation Ranch Hand

The article written by AFHS authors titled "Serum dioxin, chloracne, and acne in veterans of Operation Ranch Hand" studied the relation between categorized dioxin and the prevalence of acne for participants who attended the 1982, 1985, 1987, or 1992 follow-up examination (7). None of the Ranch Hand veterans was diagnosed with chloracne and, therefore, analyses were restricted to acne. No meaningful or consistent association between dioxin exposure and prevalence of acne with and without regard to anatomical location was observed. Results suggested that exposure of Ranch Hand veterans to dioxin was insufficient for the production of chloracne, or perhaps the exposure may have caused chloracne that resolved and was thus undetectable.

9.9. CONCLUSION

No evidence of chloracne was observed among AFHS participants, nor was any found after a medical records review. The article covering 1982 through 1992 examination attendees found no meaningful or consistent association between dioxin exposure and prevalence of acne. At the 2002 examination, the occurrence of self-reported acne after service in SEA increased in Ranch Hand enlisted groundcrew. The occurrence and duration of reported acne since service in SEA increased in background, low and high Ranch Hand dioxin categories. However, no objective physical evidence of an increase was seen. Overall, no consistent dermatological findings were noted between Ranch Hands and Comparisons and dioxin levels. Results suggested that exposure was insufficient to produce chloracne or perhaps the exposure may have caused chloracne that resolved and was undetectable at the AFHS examinations.

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10. ENDOCRINOLOGY ASSESSMENT

10.1. INTRODUCTION

The human endocrine system generally is not believed to be a primary target of dioxin or dioxin-like exposure, although large doses of dioxin are known to produce a variety of metabolic phenomena in a number of species of experimental animals. Several sites of endocrine activity, including the pancreas, thyroid gland, and hypothalamic-pituitary-testis axis, have been evaluated for dioxin toxicity in animal and human studies. Special emphasis has been placed on the parameters associated with diabetes in the AFHS due to the associations found in the analysis of the 1987, 1992, 1997, and 2002 follow-up examinations.

The AFHS endocrinology assessment for the 1982, 1985, 1987, 1992, 1997, and 2002 follow-up examinations (1-7) included medical records verification of questionnaire responses, physical examination results, and laboratory findings.

10.2. TYPE 2 DIABETES

Type 2 diabetes, the diagnosis given to approximately 90 percent of all diabetics in the general population, describes a combination of insulin resistance, insulin deficiency, and glucose overproduction. The two most important hormones secreted by the pancreas are insulin and glucagon. Insulin stimulates liver cells to take up glucose from the blood and convert it into glycogen. Glucagon stimulates the conversion of glycogen into glucose, which is then released into the blood. The production of insulin is regulated by blood glucose concentrations; high blood glucose concentrations combined with insulin deficiency results in diabetes. The epidemiologic studies suggest that any increased risk of type 2 diabetes from herbicide or dioxin exposure is small when compared to known risk factors, such as family history, obesity, and physical inactivity.

Glucose [at 1987 through 2002 follow-up examinations], urinary glucose (presence or absence) [at 1992 and 1997 follow-up examinations], serum insulin (fasting for all participants and 2-hour postprandial for nondiabetics) [at the 1992 through 2002 examinations], and glucagons [at the 1992 follow-up examination] were analyzed.

C-peptide is a subunit of insulin and is measured to differentiate insulin production by the body and insulin injected into the body. The C-peptide level may be measured in a patient with type 2 diabetes to see if the body is still producing any insulin. It may also be measured in the evaluation of low blood sugar to see if a patient is producing too much insulin. C-peptide was analyzed at the 1992 and 2002 follow-up examinations for participants classified as diabetic.

Proinsulin is a precursor of insulin with minimal hormonal activity and is converted into insulin by enzymatic action. Proinsulin was analyzed at the 1992 and 2002 follow-up examinations for participants classified as diabetic.

Hemoglobin A1c indicates a patient's blood sugar control over the last 2 to 3 months. Hemoglobin A1c is formed when glucose in the blood binds irreversibly to hemoglobin to form a stable glycated hemoglobin complex and is not subject to the fluctuations that are seen with daily blood glucose monitoring. Hemoglobin A1c was analyzed at the 1992 through 2002 follow-up examinations for participants classified as diabetic.

Glutamic acid decarboxylase antibodies (GADA) (presence or absence) was analyzed at the 2002 follow-up examination for participants classified as diabetic. Two-hour postprandial glucose was measured at all six physical examinations on nondiabetics. Two-hour postprandial urinary glucose was measured at the 1992 through 2002 examinations on all nondiabetics.

As part of the health interview questionnaire, questions were asked of diabetics regarding the use of insulin, oral diabetes medication, and diet. This self-reported information was verified and a diabetic control index was constructed and analyzed for all participants at the 1992 through 2002 follow-up examinations. This index was categorized as "requiring insulin," "oral hypoglycemics," "diet and exercise," or "no treatment" for diabetics and "no diabetes" for nondiabetics.

A variable that was termed "time-to-diabetes onset" was analyzed at the 1992 through 2002 follow-up examinations. This variable combined both diabetics and nondiabetics. For the purposes of statistical analyses, time-to-diabetes onset was the number of years between the date of diagnosis of diabetes and the end date of the last qualifying tour of duty in SEA for diabetics. For nondiabetics, this variable was the number of years between the date of the AFHS physical examination and the end date of the last qualifying tour of duty in SEA.

For the 2002 follow-up examination, the American Diabetes Association's (ADA) revised definition of a diabetic was used (8). According to the ADA, a diabetic is defined as an individual with a 2-hour postprandial glucose level of 200 mg/dL or greater on two separate occasions, or a fasting glucose level of 126 mg/dL or greater on two separate occasions, or one 2-hour postprandial glucose level of 200 mg/dL or greater and a fasting glucose level of 126 mg/dL or greater on separate occasions. In addition, any participant diagnosed as a diabetic prior to the 2002 examination was included in the analysis.

Participants were considered diabetics at 1985, 1987, 1992 and 1997 AFHS examinations if they had a 2-hour postprandial glucose level of 200 mg/dL or greater at that physical examination or a verified history of diabetes prior to that examination.

At the 1992 follow-up examination diabetic retinopathy and neuropathy (presence or absence) were assessed.

AFHS staff and their colleagues wrote the following journal articles on diabetes and glucose control:

- Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand (9) and a follow-up letter to the editor (10)
- Letter to the Editor: Weight history, glucose intolerance, and insulin levels in middle-aged Swedish men (11)
- Serum dioxin, insulin, fasting glucose and sex hormone-binding globulin in veterans of Operation Ranch Hand (12)
- Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background levels of exposure (13)
- Dioxin and diabetes mellitus: An analysis of the combined NIOSH and Ranch Hand data (14)
- Diabetes mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin elimination in veterans of Operation Ranch Hand (15)
- Insulin sensitivity following Agent Orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (16).
- A Matched Analysis of Diabetes Mellitus and herbicide exposure in veterans of Operation Ranch Hand (17)

The 2000 through 2004 IOM reports found limited or suggestive evidence of an association between exposure to herbicides, including 2,4,5-T and its contaminant dioxin, and type 2 diabetes (18-20).

10.3. THYROID

The thyroid gland produces thyroxine (T_4) and triiodothyronine (T_3) hormones that are released in response to thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. To maintain thyroid hormone homeostasis, the pituitary is stimulated to release more TSH when circulating T_3 and T_4 levels are low. Conversely, high levels of circulating T_3 and T_4 trigger the pituitary to reduce TSH production. Disruptions in this feedback loop can lead to diseases such as hypothyroidism and hyperthyroidism.

The AFHS health interview questionnaires posed a general screening question on thyroid function and disease. Each participant was asked the following question during the in-person health interview: "Since the date of the last interview, has a doctor told you for the first time that you had thyroid problems?" A medical records review was accomplished to confirm self-reported problems with thyroid function and to identify any unreported thyroid conditions. At the 1985 through 2002 follow-up physical examinations, a history of thyroid disease was constructed for each participant.

The physical examination of endocrine function included manual palpation of the thyroid gland for the 1985 through 2002 follow-up physical examinations. Thyroid abnormalities included an enlarged gland, tenderness, presence of nodules, or a thyroidectomy.

Laboratory measurements obtained at various examinations (examination given in parentheses) included antithyroid antibodies (1992, 1997, 2002), TSH (1985-2002), free T_4 (2002), T_4 total (1982, 1992, 1997), T_3 uptake (1982-1987). A free thyroxine index (1982) (a mathematical computation from T_4 and T_3 uptake that estimates how much thyroid hormone is free in the blood stream) was analyzed at the 1982 examination only.

The following journal article on the thyroid function was written by AFHS staff and their colleagues:

- Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels and thyroid function in Air Force veterans of the Vietnam War (21).

In the 2002 update, the IOM Committee concluded that there is inadequate or insufficient evidence to determine if an association exists between Agent Orange and other herbicides used in Vietnam and altered thyroid function (22). This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (20).

10.4. HYPOTHALAMIC-PITUITARY-TESTIS AXIS

The hypothalamic-pituitary-testis axis produces several hormones affecting gonadal function. The hypothalamus releases gonadotropin-releasing hormone that subsequently signals the pituitary to release luteinizing hormone (LH), the hormone that regulates growth and development of eggs and sperm. Within the testis, LH stimulates testosterone production in the Leydig cells. Testosterone from the testes, as well as follicle-stimulating hormone (FSH) released by the pituitary, stimulates production of sperm. Excess testosterone converts to estradiol by the aromatase enzyme. Male-mediated adverse reproductive effects can be due to any number of imbalances in gonadal hormones produced via the hypothalamic-pituitary-testis axis.

The 1985, 1987, 1997, and 2002 physical examinations included evaluation of the testes by manual palpation. Testicular abnormalities evaluated included absent or atrophic testes. Testicular volume (minimum and total) was determined using ultrasound techniques for the 1992 follow-up examination.

Laboratory measurements assessed at various examinations (examinations given in brackets) included total testosterone [1982-2002], free testosterone [1992-2002], lutenizing hormone (LH) [1992-2002], follicle-stimulating hormone (FSH) [1987-2002], estradiol [1992-2002], and sex hormone-binding globulin (SHBG) [1992] were collected and analyzed for all participants in the endocrinology assessment. A total testosterone to SHBG ratio was analyzed for the 1992 AFHS examination only.

Three cortisol measurements were accomplished at the 1985 follow-up examination; 2-hour cortisol, differential cortisol, and initial cortisol. The two-hour cortisol measurements were considered a general indicator of the integrity of the endocrine system and as a secondary risk factor for coronary heart disease.

AFHS staff and their colleagues wrote the following journal articles on testosterone, FSH, LH, testicular abnormalities, sperm count, sperm abnormalities, and testicular volume:

- Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand (23)
- Letter to the editor: Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand (24).

Based on the 2004 *Veterans and Agent Orange* update (20), "the lack of data on the association between exposure to the chemicals of interest and altered sperm characteristics or infertility, coupled with the lack of exposure information on Vietnam veterans, precludes quantification of any possible increase in their risk."

10.5. ENDOCRINOLOGY VARIABLES

The following chart lists the variables that were analyzed for the endocrinology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Diabetes and Glucose Control							
C-peptide					**X**		X
Diabetes, Prevalence		X	X	**X**	**X**	**X**	**X**
Diabetes, Time to Onset					**X**	**X**	**X**
Diabetic Control					**X**	**X**	**X**
Diabetic Neuropathy					X		
Diabetic Retinopathy					X		
Glucose, 2-hour Postprandial	X	X	X	**X**	**X**	X	X
Glucose, 2-hour Postprandial Urinary					**X**	**X**	**X**
Glucose, Fasting				**X**	**X**	**X**	X
Glucose, Fasting Urinary					**X**	**X**	
GADA							X
Glucagon					**X**		
Hemoglobin A1c					**X**	**X**	**X**
Insulin					**X**	X	**X**

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Proinsulin					**X**		X
Thyroid							
Antithyroid Antibodies					**X**	X	X
Free Thyroxine Index	X						
T_3 Uptake	X	X	X	X			
T_4, Free							X
T_4, Total	X				**X**	X	
Thyroid Disease		X	X	X	**X**	X	X
Thyroid Gland		X	X	X	X	X	X
TSH		**X**	**X**	X	X	**X**	**X**
Hypothalmic-Pituitary-Testis Axis							
Cortisol, 2-hour		X					
Cortisol, Differential		**X**					
Cortisol, Initial		X					
Estradiol					**X**	X	X
FSH			X	**X**	**X**	X	X
LH					**X**	X	**X**
SHBG					X		
Testicular Examination		X	X	**X**		X	X
Testicular Volume (Minimum and Total)					**X**		
Testosterone, Free					X	X	**X**
Testosterone, Total	X	X	X	**X**	**X**	X	X
Total Testosterone to SHBG Ratio					X		

10.6. DIABETES AND GLUCOSE CONTROL

10.6.1. C-peptide

The analysis of the 1992 follow-up examination data showed that Ranch Hands in the low dioxin category had a higher average C-peptide level than Comparisons among diabetic enlisted groundcrew. In addition, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high C-peptide levels than Comparisons, primarily among older diabetic participants.

10.6.2. Diabetes, Prevalence

A higher percentage of Ranch Hands in the high dioxin category than Comparisons were diabetic in the analysis of the 1987 follow-up examination data. This difference was seen primarily in older participants. The percentage of diabetic Ranch Hands also increased with increasing initial and 1987 dioxin levels.

Among officers, the analysis of the 1992 follow-up examination data showed a higher prevalence of diabetes among Ranch Hands in the combined low and high dioxin category than Comparisons. The prevalence of Ranch Hand diabetics also increased with increasing initial dioxin and 1987 dioxin levels.

A higher percentage of Ranch Hands in the high dioxin category than Comparisons were diabetic at the 1997 follow-up examination. The prevalence of Ranch Hand diabetics also increased with increasing initial dioxin and 1987 dioxin levels.

In the analysis of the 2002 follow-up examination data, the percentage of participants classified as diabetic increased as initial and 1987 dioxin levels increased.

10.6.3. Diabetes, Time to Onset

The analysis of 1992 follow-up examination data found that the time-to-diabetes onset decreased with increasing 1987 dioxin levels. The time-to-diabetes onset decreased with increasing initial and 1987 dioxin levels in the 1997 and 2002 follow-up examination data analyses.

10.6.4. Diabetic Control

Analysis of 1992 follow-up examination data showed that the percentage of Ranch Hands using oral hypoglycemics to control diabetes increased with increasing initial dioxin levels and with 1987 dioxin levels, particularly among enlisted flyers and enlisted groundcrew. Ranch Hands in the high dioxin category had a higher prevalence of oral hypoglycemic use for diabetes than Comparisons. The percentage of Ranch Hands controlling diabetes through diet only increased with increasing 1987 dioxin levels, particularly among officers and enlisted flyers.

The percentage of Ranch Hands requiring insulin to control diabetes was greater than Comparisons in the analysis of the 1997 follow-up examination data. The percentage of Ranch Hands in both the low and high dioxin categories requiring insulin for diabetic control also was greater than Comparisons. The percentage of Ranch Hands requiring insulin increased with increasing initial dioxin levels. In addition, the percentage of Ranch Hands using diet only to control diabetes and the percentage of Ranch Hands using oral hypoglycemics for diabetic control increased with increasing 1987 dioxin levels.

Analysis of the 2002 follow-up examination data showed that the percentage of Ranch Hands requiring insulin increased with increasing initial and 1987 dioxin levels. A higher percentage of Ranch Hands in the high dioxin category than Comparisons required insulin. In addition, the percentage of Ranch Hands using oral hypoglycemics for diabetic control increased with increasing 1987 dioxin levels.

10.6.5. Glucose, 2-hour Postprandial

In the analysis of the 1987 follow-up examination data, 2-hour postprandial glucose levels in Ranch Hands increased with increasing initial dioxin levels and with 1987 dioxin levels in Ranch Hands with earlier tours. In addition, abnormally high 2-hour postprandial glucose levels were more prevalent among Ranch Hands in the high dioxin category than among Comparisons.

The analysis of 1992 follow-up examination data showed that Ranch Hands had higher average 2-hour postprandial glucose levels than Comparisons among obese (approximate body mass index of 30 or more) participants, among obese enlisted groundcrew, and among enlisted groundcrew with no family history of diabetes. Ranch Hands in the high dioxin category had higher average 2-hour postprandial glucose levels than Comparisons among obese participants and among participants with no family history of diabetes. A greater percentage of Ranch Hands in the high dioxin category than Comparisons also had elevated 2-hour postprandial glucose levels.

Two-hour postprandial glucose levels at the 1992 follow-up examination increased with increasing initial dioxin levels. An increase in 2-hour postprandial glucose levels with increasing 1987 dioxin levels was observed, as was the prevalence of elevated 2-hour postprandial glucose among non-Black participants.

10.6.6. Glucose, 2-hour Postprandial Urinary

Based on the analysis of the 1992 follow-up examination data, the prevalence of abnormal 2-hour postprandial urinary glucose levels in nondiabetic Ranch Hands increased with increasing 1987 dioxin levels.

Among nondiabetic officers, a higher percentage of Ranch Hands than Comparisons had 2-hour postprandial urinary glucose present at the 1997 and 2002 follow-up examination.

10.6.7. Glucose, Fasting

In the analysis of the 1987 follow-up examination data, fasting glucose levels in Ranch Hands increased with increasing initial and 1987 dioxin levels. Similarly, the percentage of Ranch Hands with abnormally high fasting glucose levels increased with increasing initial dioxin and with 1987 dioxin levels. The average fasting glucose level was greater for Ranch Hands in the high dioxin category than for Comparisons, as was the prevalence of abnormally high fasting glucose levels.

The 1992 follow-up examination showed that fasting glucose levels in Ranch Hands increased with increasing initial dioxin, particularly among officers and enlisted groundcrew. Among only nondiabetic participants, fasting glucose levels increased with increasing initial dioxin among Ranch Hand officers. Fasting glucose levels increased with increasing 1987 dioxin when evaluating all Ranch Hands and also when analysis was restricted to only diabetic Ranch Hands. In addition, the prevalence of abnormally high fasting glucose levels in Ranch Hands increased with increasing 1987 dioxin. Nondiabetic Ranch Hands in the background dioxin category had a higher average fasting glucose level than nondiabetic Comparisons among enlisted groundcrew.

Fasting glucose levels and the prevalence of Ranch Hands with abnormally high fasting glucose levels increased with increasing initial dioxin and 1987 dioxin in the analysis of the 1997 follow-up examination data.

10.6.8. Glucose, Fasting Urinary

The analysis of the 1992 follow-up examination data showed that the percentage of Ranch Hands with fasting urinary glucose present increased with increasing initial dioxin and with 1987 dioxin, both when all participants were considered and when diabetic participants only were considered.

In the analysis of the 1997 follow-up examination data, the percentage of Ranch Hands (diabetic and nondiabetic combined) with fasting urinary glucose present increased with increasing 1987 dioxin.

10.6.9. Glucagon

In the 1992 follow-up examination data analysis, serum glucagon levels increased in Ranch Hands as 1987 dioxin increased, particularly among Ranch Hands with no family history of diabetes. The percentage of Ranch Hands with an abnormally high glucagon level also increased as 1987 dioxin increased. Among all participants who treated their diabetes through diet only, and among officers who did the same, Ranch Hands had a higher average serum glucagon level than Comparisons when diabetic participants were analyzed separately. When nondiabetics were analyzed separately, serum glucagon levels increased in Ranch Hands as initial and 1987 dioxin levels increased.

10.6.10. Hemoglobin A1c

Hemoglobin A1c levels increased with increasing initial dioxin levels among Ranch Hand officers and enlisted groundcrew in the analysis of the 1992 follow-up examination data. The percentage of Ranch Hand officers with abnormally high hemoglobin A1c levels also increased with increasing initial dioxin levels. In addition, an increase in hemoglobin A1c levels with increasing 1987 dioxin levels was observed among all Ranch Hands, older obese Ranch Hands, and diabetic Ranch Hands. Among obese Ranch Hands, the prevalence of abnormally high hemoglobin A1c levels increased with increasing 1987 dioxin levels.

Ranch Hands in the high dioxin category had increased average hemoglobin A1c levels and a greater prevalence of abnormally high hemoglobin A1c levels than Comparisons when the 1997 follow-up examination data were analyzed. In addition, hemoglobin A1c levels increased with increasing 1987 dioxin levels in Ranch Hands, and the percentage of Ranch Hands with abnormally high hemoglobin A1c levels increased with increasing 1987 dioxin levels.

In the analysis of the 2002 follow-up examination data, the prevalence of abnormally high hemoglobin A1c levels in Ranch Hand diabetics increased with increasing 1987 dioxin levels.

10.6.11. Insulin

Based on the analysis of all participants, the 1992 follow-up examination data analysis showed a higher average insulin level in Ranch Hands than in Comparisons among obese participants and obese officers. Insulin levels in Ranch Hands increased with increasing 1987 dioxin levels. The prevalence of abnormally high insulin levels was greater in Ranch Hands than in Comparisons among obese officers and among obese participants in the background dioxin category.

The 1992 follow-up examination analysis of diabetic participants showed that the average serum insulin level was higher for Ranch Hands in the low dioxin category than for Comparisons. Among older diabetic participants, the prevalence of abnormally high insulin levels was higher for Ranch Hands in the low dioxin category than for Comparisons.

The 1992 follow-up examination analysis of nondiabetic participants showed a higher average serum insulin level for Ranch Hands than Comparisons among obese participants. Serum insulin levels for nondiabetic Ranch Hand participants increased with increasing initial and 1987 dioxin levels. The prevalence of abnormally high serum insulin levels in Ranch Hands increased with increasing 1987 dioxin and initial dioxin levels, particularly among enlisted flyers. Also among enlisted flyers, Ranch Hands in the high dioxin category had a higher prevalence of abnormally high serum insulin levels than Comparisons.

Data for both fasting (for all participants) and 2-hour postprandial insulin (for nondiabetics) were collected for the 2002 follow-up examination data. Fasting insulin levels and the prevalence of abnormally high fasting insulin levels increased in Ranch Hands as initial dioxin increased.

10.6.12. Proinsulin

The 1992 follow-up examination analysis of diabetic Ranch Hands showed that the percentage of Ranch Hand officers with abnormally high serum proinsulin levels increased with increasing 1987 dioxin levels.

10.7. ARTICLES

10.7.1. Serum Dioxin and Diabetes Mellitus in Veterans of Operation Ranch Hand

The prevalence of diabetes, use of oral medications to control diabetes, and time-to-diabetes onset were studied, based on participants who had a dioxin measurement and attended the 1982, 1985, 1987, or 1992 AFHS examination (9). Analysis also was conducted on glucose levels and serum glucose abnormalities based on participants at the 1992 physical examination who had a dioxin measurement. Each Ranch Hand veteran was assigned to the background, low or high dioxin exposure category on the basis of a measurement of dioxin body burden. Glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased, and time-to-diabetes-onset decreased, with dioxin exposure. Serum insulin abnormalities for Ranch Hands in the high dioxin category were increased in nondiabetics. The results indicated a possible relation between dioxin exposure and diabetes mellitus, glucose metabolism, and insulin production.

10.7.2. Letter to the Editor: Serum Dioxin and Diabetes Mellitus in Veterans of Operation Ranch Hand

Subsequent to the publication of the above article (9), the possibility of an interaction between plasma lipid fractions, diabetes, and total serum dioxin levels was raised. The concern was that dioxin might be more heavily concentrated in the triglyceride fraction of total lipids, which would contribute to the finding of increased risk of diabetes mellitus in participants with high dioxin levels because diabetes is associated with increased triglycerides. The AFHS authors conducted further analysis and found no evidence to support this concern (10).

10.7.3. Letter to the Editor: Weight History, Glucose Intolerance, and Insulin Levels in Middle-aged Swedish Men

A 1998 article described the relation between impaired glucose tolerance and type 2 diabetes mellitus and the length of time that a subject had been overweight (25). Duration of being overweight was studied as an independent risk factor for impaired glucose tolerance and type 2 diabetes mellitus using data from the 1992 AFHS follow-up examination (11). The relation of body mass index and waist circumference to risk of impaired glucose tolerance or diabetes mellitus generally agreed between the two articles. Duration of being overweight, however, was not seen as an independent risk factor.

10.7.4. Serum Dioxin, Insulin, Fasting Glucose and Sex Hormone-Binding Globulin in Veterans of Operation Ranch Hand

Insulin, fasting glucose, and SHBG were analyzed in relation to dioxin based on participants at the 1992 physical examination who had a dioxin measurement (12). Each Ranch Hand veteran was assigned to one of three dioxin categories—background, low, and high—based on his dioxin level. Among nondiabetic veterans, insulin was increased for Ranch Hands in the high dioxin category. Insulin decreased as SHBG increased among young (age 53 or less), lean (body mass index < 30), nondiabetic veterans in the high category. The findings suggested a compensatory metabolic relation between dioxin and insulin regulation.

10.7.5. Serum Dioxin Level in Relation to Diabetes Mellitus among Air Force Veterans with Background Levels of Exposure

Data from several epidemiologic studies suggest that exposure to unusually high amounts of dioxin increased the risk of diabetes mellitus, and experimental data suggest that the mechanism for this is decreased cellular glucose uptake. To investigate the dose response relation more closely, the association of serum dioxin level with prevalence of diabetes mellitus and with levels of serum insulin and glucose was examined among 1,197 Comparison veterans who attended the 1992 physical examination; and whose serum dioxin level were within the range of background exposure typically seen in the United States (≤10 ng/kg lipid) (13). The prevalence of diabetes was increased for those veterans who were in the highest quartile of dioxin levels (≥5.2 ng/kg lipid), as compared to veterans in the first quartile of dioxin levels (<2.8 ng/kg lipid). The association was slightly weaker after adjusting for serum triglycerides drawn at the same time of the dioxin measurement. A positive relation existed between glucose and insulin levels and serum dioxin; adjustment for serum triglycerides again weakened most of the associations. Whether adjustment for serum triglycerides was appropriate, however, could not be determined with the available data. The association of background-level dioxin exposure with the prevalence of diabetes in these data may well be due to reasons other than causality, although a causal contribution could not be wholly dismissed.

10.7.6. Dioxin and Diabetes Mellitus: An Analysis of the Combined NIOSH and Ranch Hand Data

In an attempt to reconcile disparate results, analysis was conducted combining AFHS and National Institute for Occupational Safety and Health (NIOSH) data sets, the two principal studies of dioxin and diabetes. A uniform approach to outcome definition, data analysis, and covariate control was adopted, and results were described in a 2001 journal article (14). This article reanalyzed data from 990 Ranch Hands and 1,275 Comparisons and a NIOSH population of 267 chemical workers and 227 referents. The Ranch Hand veterans had lower concentrations of lipid-adjusted serum dioxin (median 12 ppt) than the NIOSH workers (median 75 ppt). The combined exposed groups did not differ markedly from the combined nonexposed groups for prevalence of diabetes, with no evidence of a difference of exposure effect between studies. In addition, virtually no difference between combined exposed and nonexposed groups in average fasting serum glucose, and there was little evidence in either study of a dose-response trend for fasting serum glucose. An increasing trend was found in prevalence of diabetes with increased dioxin among the Ranch Hand population, with excess risk largely confined to the highest 8 percent of the exposed group (>78 ppt serum dioxin) versus those with less than 10 ppt dioxin. No such positive dose-response was found in the NIOSH population. The reason for the difference in diabetes dose-response trends between the two studies was unknown.

10.7.7. Diabetes Mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin Elimination in Veterans of Operation Ranch Hand

Reviewers of AFHS results on diabetes hypothesized that the association between diabetes and dioxin concentration reflects an association between diabetes and the dioxin elimination rate. Individuals with slow elimination rates may retain dioxin for a longer period of time, have a long dioxin half-life, and, consequently, may be at an increased risk for diabetes. Individuals with quick elimination rates may retain dioxin for a shorter period of time, have a relatively short dioxin half-life, and may be at a decreased risk for diabetes (15). Researchers analyzed data derived from a pharmacokinetic study of dioxin elimination in Ranch Hand veterans who had four repeated dioxin measurements from blood collected during physical examinations in 1982, 1987, 1992, and 1997. The authors found no relation between the rate of dioxin elimination and the occurrence or time to onset of diabetes. Without adjustment for age, body mass index, family history of diabetes, and smoking history, the time to onset of diabetes decreased and the risk of diabetes increased with a diminished elimination rate. After adjustment, diabetes, time to onset and occurrence were not associated with dioxin elimination. No difference was found between the average elimination rates of diabetic and nondiabetic veterans, without or with adjustment for risk factors.

10.7.8. Insulin Sensitivity Following Agent Orange Exposure in Vietnam Veterans with High Blood Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin

Studies to determine whether insulin sensitivity was related to dioxin were performed and reported in a 2004 journal article (16). Ranch Hand and Comparison subjects were matched by age, body mass index, race, and a family history of diabetes. To determine insulin sensitivity researchers frequently sampled intravenous glucose tolerance test in a matched study of 29 Ranch Hand-Comparison pairs selected based on attendance at the 1997 examination and a quantitative insulin sensitivity check index based on fasting glucose and fasting insulin in 71 matched pairs who attended the 2002 examination. There were no differences in an insulin sensitivity index, a quantitative insulin sensitivity check index, tumor necrosis factor alpha, adiponectin, and two measures of insulin secretion between Ranch Hands and Comparisons. The difference in the insulin sensitivity index and the quantitative insulin sensitivity check index between the Ranch Hand member and the Comparison member of the pair decreased as the difference in dioxin increased. These data suggested that high blood dioxin levels may promote an insulin-resistant

state, but the magnitude of this effect appeared to be small, such that an 18-fold increase in dioxin due to increased exposure resulted in only a 10 percent change in the insulin sensitivity index in the 29 matched pairs.

10.7.9. A Matched Analysis of Diabetes Mellitus and Herbicide Exposure in Veterans of Operation Ranch Hand

The authors reanalyzed Ranch Hand data in an attempt to understand the check mark pattern first observed in the AFHS in 1991. The checkmark pattern described the following pattern: although the risk of diabetes was increased in Ranch Hand veterans in the highest exposure category, there was no overall increase in diabetic risk and the risk was decreased among those with background levels of serum dioxin. Data used for these analyses were from 1987, 1992, and 1997 physical examinations. An analysis based on individual one-to-one matching on year of birth, race, military occupation, family history of diabetes, and percent body fat during service in SEA (within 1%) found increased risk of diabetes in all Ranch Hands, and increased risk in all three Ranch Hand exposure categories. These data also suggested that a previously observed 'check mark' pattern of decreased risk at low dioxin levels and an increased risk at high levels may have been artifactual. (17)

10.8. THYROID

10.8.1. Antithyroid Antibodies

Ranch Hands in the combined low and high dioxin category had a higher prevalence of antithyroid antibodies than Comparisons, based on analysis of the 1992 follow-up examination data.

10.8.2. Thyroxine (T_4), Total

In the analysis of the 1992 follow-up examination data, the percentage of abnormally high T_4 levels increased with increasing initial and 1987 dioxin levels.

10.8.3. Thyroid Disease

In the 1992 follow-up examination analysis of thyroid disease, among participants with type A personalities, a higher percentage of Ranch Hands in the background dioxin category had a history of thyroid disease than Comparisons.

10.8.4. Thyroid-stimulating Hormone (TSH)

A higher average TSH level in Ranch Hands than Comparisons was observed at the 1985 follow-up examination.

Ranch Hands in the high dioxin category had a higher average TSH level than Comparisons at the 1987 follow-up examination.

Based on data from the 1997 follow-up examination, a greater percentage of Ranch Hand enlisted groundcrew than Comparison enlisted groundcrew had an abnormally high TSH value.

The analysis of the 2002 follow-up examination data showed that the average TSH level was higher for Ranch Hands than Comparisons, primarily among officers. Ranch Hands in the background dioxin category also had a higher average TSH level than Comparisons.

10.8.5. Article

10.8.5.1. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (Dioxin) Levels and Thyroid Function in Air Force Veterans of the Vietnam War

Potential health effects of dioxin concentration on total T_4, TSH, T_3 uptake, the free thyroxine index, and thyroid diseases were examined in an AFHS article published in 2003 (21). Data for 1,009 Ranch Hand and 1,429 Comparison veterans compliant to any of the AFHS examinations in 1982, 1985, 1987, 1992, and 1997 were analyzed. Each veteran was assigned to one of four dioxin categories: Comparison, background Ranch Hand, low Ranch Hand, or high Ranch Hand. The 1982, 1985, 1987, 1992, and 1997 AFHS examinations showed a trend of increasing TSH that was not accompanied by changes in circulating T_4 or in the percentage of T_3, which was measured only in 1982 and 1985. Ranch Hands in the low and high dioxin categories had a greater TSH average than Comparisons, and a trend test showed a linear increase across the Comparison, background, low, and high dioxin categories. There was no evidence of change in clinical thyroid disease, and no changes in microsomal or antithyroidal antibodies were observed. These findings suggested that exposure to dioxin can affect thyroid pituitary axis leading to increased TSH levels.

10.9. HYPOTHALAMIC-PITUITARY-TESTIS AXIS

10.9.1. Differential Cortisol

Younger Black Ranch Hands had a lower average differential cortisol level than their Comparison counterparts at the 1985 follow-up examination.

10.9.2. Estradiol

The analysis of the 1992 follow-up examination data found that the percentage of abnormally high estradiol levels increased with increasing 1987 dioxin levels among Ranch Hand enlisted groundcrew.

10.9.3. Follicle-stimulating Hormone (FSH)

The 1987 follow-up examination data analysis showed that FSH levels increased with increasing 1987 dioxin levels among Ranch Hands with later tours of duty. In the analysis of the 1992 follow-up examination data, a higher percentage of Ranch Hand officers had abnormally high FSH levels relative to Comparison officers.

10.9.4. Luteinizing Hormone (LH)

The percentage of Ranch Hands at the 1992 follow-up examination with abnormal high LH levels increased with increasing initial dioxin levels. In addition, Ranch Hands in the low dioxin category had a higher average LH level than Comparisons.

In the analysis of 2002 follow-up examination data, Ranch Hand officers had a higher average LH level than Comparison officers did. Ranch Hands in the low dioxin category also had a higher average LH level than Comparisons.

10.9.5. Testicular Examination

In the analysis of the 1987 follow-up examination data, the percentage of Ranch Hands with an abnormal testicular examination increased with increasing initial and 1987 dioxin levels. In addition, more Ranch Hands in the high dioxin category had an abnormal testicular examination than Comparisons.

10.9.6. Testicular Volume (Minimum and Total)

In the 1992 follow-up examination data analysis, the minimum testicular volume, using ultrasound techniques, decreased as 1987 dioxin levels increased among Ranch Hand enlisted flyers. Total testicular volume, using ultrasound techniques, decreased with increasing levels of initial and 1987 dioxin among Ranch Hand enlisted flyers.

10.9.7. Testosterone, Free

In the 2002 follow-up examination data analysis, Ranch Hand officers were found to have had a higher percentage of abnormally low free testosterone levels than Comparison officers.

10.9.8. Testosterone, Total

The analysis of the 1987 follow-up examination data found that testosterone levels decreased with increasing 1987 dioxin levels in Ranch Hands with later tours of duty. Testosterone levels also decreased with increasing initial dioxin levels, particularly among Ranch Hands with type A personalities at the 1987 follow-up examination. In addition, Ranch Hands in the high dioxin category had a lower average testosterone level than Comparisons. Among participants with type A personalities, the prevalence of abnormally low testosterone levels was greater in Ranch Hands in the high dioxin category than in Comparisons.

In the analysis of 1992 follow-up examination data, testosterone levels decreased with increasing 1987 dioxin among all Ranch Hands, Ranch Hand officers and enlisted flyers. Among Ranch Hands with type A personalities, testosterone levels decreased with increasing initial dioxin levels. The percentage of Ranch Hand officers with abnormally low testosterone levels increased as initial and 1987 dioxin levels increased. In addition, among participants with type A personalities, Ranch Hands in the background and low dioxin categories had a greater percentage of abnormally low testosterone levels than Comparisons.

10.9.9. Articles

10.9.9.1. Serum Dioxin, Testosterone, and Gonadotropins in Veterans of Operation Ranch Hand

Using data from the 1982, 1987, and 1992 examinations, the relations between dioxin and current testosterone, FSH, LH, testicular abnormalities, sperm count, sperm abnormalities, and testicular volume were studied (24). No consistent or meaningful association between dioxin levels and any of these outcome variables were found. The authors noted that, if adverse effects did exist, the Ranch Hand exposure in SEA was insufficient to produce detectable associations comparable with those seen in industrial workers with heavier exposure.

10.9.9.2. Letter to the editor: Serum dioxin, Testosterone, and Gonadotropins in Veterans of Operation Ranch Hand

Reviewers of the aforementioned article commented that analyses on testosterone, FSH, and LH in their continuous form were not mentioned.

In a follow-up letter to the editor (24), the AFHS authors confirmed that analyses had been conducted on the continuous form of testosterone, FSH, and LH. Findings from these analyses were weak and inconsistent with known exposure differences in Ranch Hands by military occupation. The authors noted that there may be a subclinical relation between dioxin and testosterone but the association, if it exists, was too weak to be clinically meaningful.

10.10. CONCLUSION

Results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent adverse relation between dioxin levels and diabetes. Although the prevalence of diabetes was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. Increased risks of diabetes were found with initial dioxin, in the high dioxin category, and with 1987 dioxin levels. An increase in severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and hemoglobin A1c also were observed as initial and 1987 dioxin levels increased.

The journal articles also showed glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased, and time-to-diabetes-onset decreased with dioxin exposure. Serum insulin abnormalities for Ranch Hands in the high dioxin category were increased in nondiabetics. Most of the significant relative risks described in the reports were less than 2.0. In the small matched pairs study (16), it was estimated that an 18-fold increase in dioxin would be associated with a 10 percent change in the insulin sensitivity index.

There were no consistent or meaningful associations between dioxin levels and the hypothalamic-pituitary-testis axis. The reports found no consistent associations between dioxin levels and thyroid. Although the article (21) found no evidence of clinical thyroid disease and no changes in microsomal or antithyroidal antibodies, there was trend of increasing TSH across the Comparison, background, low, and high dioxin categories.

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11. GASTROINTESTINAL ASSESSMENT

11.1. INTRODUCTION

A wealth of dioxin research data is available in animal models, but there is relatively little information about the effects of dioxin on the human digestive system. In laboratory animals, the liver is a major target organ for dioxin and dioxin-like chemicals following single high-dose and continued low-dose exposure in laboratory animals. Porphyria cutanea tarda (PCT) is a suspected clinical endpoint following moderate to high-level exposure. Although this chapter encompasses the gastrointestinal function, the focus is primarily on liver function and associated diseases.

Analyses were performed in the gastrointestinal assessment of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7) based on medical records verification of the data collected from questionnaires, physical examination, and laboratory findings. During the health interviews for each AFHS examination, each participant was asked about the occurrence of hepatitis, jaundice, cirrhosis, enlarged liver, and other liver disorders. Medical records reviews confirmed reported conditions and identified any unreported conditions for each participant. Data from all AFHS examinations were combined to form a history of liver conditions for each participant.

Listed below, are the conditions by the examination year they were analyzed:

- 1982 baseline examination: hepatomegaly; hepatitis, jaundice and other liver disorders (included liver necrosis)
- 1985 follow-up examination: 1) cirrhosis, 2) jaundice and other liver disorders, 3) enlarged liver, and 4) hepatitis (viral and alcohol-related)
- 1987 follow-up examination: 1) viral hepatitis, 2) acute and subacute necrosis of the liver, 3) chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related), 4) liver abscess and sequelae of chronic liver disease, 5) other disorders of the liver, 6) jaundice (unspecified, not of the newborn) and 7) hepatomegaly
- 1992 follow-up examination: 1) hepatitis (non-A,B,C), 2) jaundice, 3) acute and subacute necrosis of the liver, 4) chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related), 5) liver abscess and sequelae of chronic liver disease, 6) other disorders of the liver, and 7) enlarged liver (hepatomegaly)
- 1997 follow-up examination: 1) uncharacterized hepatitis (nonABCD), 2) jaundice, 3) acute necrosis of the liver, 4) chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related), 5) liver abscess and sequelae of chronic liver disease, 6) enlarged liver and 7) other disorders of the liver
- 2002 follow-up examination: 1) uncharacterized hepatitis, 2) jaundice, 3) alcohol-related chronic liver disease and cirrhosis, 4) chronic liver disease and cirrhosis not related to alcohol, 5) liver abscess and sequelae of chronic liver disease, 6) enlarged liver (hepatomegaly), and 7) other disorders of the liver – based of self-reported conditions.

The purpose of the uncharacterized hepatitis (non-A, non-B, and non-C) category was to define a category that was neither clearly A nor B nor C, so that liver disease misdiagnosed as "viral hepatitis" could be detected. The "other liver disorders" dependent variable was a combination of hepatitis in viral diseases classified elsewhere, unspecified hepatitis, other specified diseases of the liver, unspecified

disorder of the liver, nonspecific elevation of levels of transaminase or lactate dehydrogenase (LDH), other nonspecific abnormal serum enzyme levels, and nonspecific abnormal results of liver studies.

PCT is a disorder of porphyrin metabolism that leads to massive overproduction and excretion of uroporphyrin. Uroporphyrin and coproporphyrin were analyzed at the 1982 and 1985 examinations. D-aminolevulinic acid, the first compound in the porphyrin synthesis pathway, was analyzed at the 1982 examination.

To identify any potential cases of PCT, each participant was asked the following three questions during the administration of the questionnaire: (1) "Have you had patches of your skin change color?"; (2) "Have you had easier bruising of the skin than usual?"; and (3) "Have you had skin that was extra sensitive or seemed to hurt for no reason?" Participant-reported responses to these questions on skin bruises, patches, or sensitivity were analyzed. Positive responses were considered a surrogate measure for possible PCT. The variable, Skin Bruises, Patches, or Sensitivity, was analyzed at the 1982, 1985, and 1987 follow-up examinations.

Only for the 1985 and 1987 follow-up examinations the presence of gastric, duodenal, peptic, or gastrojejunal ulcers, as verified by a review of medical records, were analyzed.

Current hepatomegaly was assessed by the AFHS examining physician at all six physical examinations.

Laboratory variables analyzed at all six examinations included alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), alkaline phosphatase, total bilirubin, direct bilirubin, LDH, cholesterol and triglycerides. Laboratory variables analyzed at the 1987 through 2002 physical examinations included creatine phosphokinase, high density lipoprotein (HDL) cholesterol, cholesterol-HDL ratio and prothrombin time. At the 1992 through 2002 physical examinations, the following laboratory variables were analyzed, stool hemoccult, serum amylase, and 10 components in a protein profile (prealbumin, albumin, α-1-acid glycoprotein, α-1-antitrypsin, α-2-macroglobulin, apolipoprotein B, C3 complement, C4 complement, haptoglobin, and transferrin).

Serological evidence of prior hepatitis A, B, and C were analyzed at the 1992 through 2002 physical examinations. Antibodies for hepatitis D and current hepatitis B were analyzed at the 1997 physical examination.

In 1987, analysis was conducted of d-glucaric acid, which is considered a reliable index of hepatic microsomal activity. The analyses were based on urine collected at the 1985 follow-up examination and stored at -70 °C.

AFHS staff and their colleagues wrote the following journal article on the relation of hepatic abnormalities and indices of hepatic function to dioxin:

- Serum dioxin and hepatic abnormalities in veterans of Operation Ranch Hand (8).

The IOM Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides reported in their 1994 publication, *Veterans and Agent Orange* (9), that there was "sufficient" evidence to establish an association between PCT and herbicides or dioxin, although not a causal relation. In the 1996 *Veterans and Agent Orange* update, the association with PCT was changed to "limited or suggestive" (10). This was also the conclusion in the 2004 *Veterans and Agent Orange* update (11).

The following chart lists the variables that were analyzed for the gastrointestinal assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Amylase, Serum					X	X	X
d-glucaric Acid				X			
Hepatitis A, Prior					X	X	X
Hepatitis B, Current						X	
Hepatitis B, Prior					**X**	X	X
Hepatitis C, Prior					X	X	X
Antibodies for Hepatitis D						X	
Hepatitis, Uncharacterized	X	X	X	**X**	X	X	X
Hepatomegaly, Current	X	X	X	X	X	X	X
Hepatomegaly (Enlarged Liver), History		X	X	X	X	X	X
Jaundice (unspecified)	X	X	X	X	X	X	X
Lipids: Cholesterol	X	X	X	**X**	**X**	X	X
Lipids: Cholesterol, HDL			X	**X**	**X**	**X**	X
Lipids: Cholesterol-HDL Ratio			X	**X**	**X**	**X**	X
Lipids: Triglycerides	X	**X**	X	**X**	**X**	**X**	**X**
Liver Abscess and Sequelae of Chronic Liver Disease			X	X	X	X	X
Liver Disease and Cirrhosis (Alcohol-related), Chronic	X	X	X	X	X	X	X
Liver Disease and Cirrhosis (Nonalcohol-related), Chronic	X	X	X	X	X	X	X
Liver Disorders, Other	X	X	X	**X**	**X**	**X**	X
Liver Enzymes: Alkaline Phosphatase	X	**X**	**X**	**X**	**X**	**X**	**X**
Liver Enzymes: ALT	X	X	X	**X**	**X**	**X**	X
Liver Enzymes: AST	X	**X**	X	X	**X**	**X**	X
Liver Enzymes: Bilirubin, Direct	X	**X**	X	**X**	X	X	X
Liver Enzymes: Bilirubin, Total	X	X	X	X	X	X	X
Liver Enzymes: Creatine Phosphokinase			X	X	**X**	**X**	X
Liver Enzymes: GGT	X	X	X	**X**	**X**	**X**	X
Liver Enzymes: LDH	X	X	X	X	**X**	X	X
Necrosis of the Liver, Acute and Subacute			X	X	X	X	X
Porphyrin Metabolism: Coproporphyrin	X	X					
Porphyrin Metabolism: d-aminolevulinic Acid	X						
Porphyrin Metabolism: Uroporphyrin	X	X					
Protein Profile: α-1-Acid Glycoprotein					**X**	**X**	X
Protein Profile: α-1-Antitrypsin					**X**	**X**	**X**
Protein Profile: α-2-Macroglobulin					**X**	**X**	X
Protein Profile: Albumin					**X**	X	X
Protein Profile: Apolipoprotein B					**X**	X	X
Protein Profile: C3 Complement					**X**	X	X
Protein Profile: C4 Complement					X	**X**	**X**
Protein Profile: Haptoglobin					**X**	**X**	**X**
Protein Profile: Prealbumin					**X**	**X**	X
Protein Profile: Transferrin					X	X	X
Prothrombin Time				**X**	**X**	X	**X**

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Skin Bruises, Patches, or Sensitivity	X	X	X	**X**			
Stool Hemoccult					**X**	X	**X**
Ulcer		X	X	X			

11.2. HEPATITIS

11.2.1. Hepatitis B, Prior

Among enlisted flyers, the occurrence of prior hepatitis B infection at the time of the 1992 follow-up examination increased with increasing 1987 dioxin levels.

11.2.2. Hepatitis, Uncharacterized (Non-A, Non-B, Non-C)

Data from the 1987 follow-up examination showed for those with earlier tours of duty an increase in the prevalence of uncharacterized hepatitis as initial dioxin levels increased and as 1987 dioxin levels increased. Ranch Hands in the high dioxin category also had a greater occurrence of uncharacterized hepatitis than Comparisons.

11.3. LIPIDS

11.3.1. Cholesterol

Ranch Hands at the 1987 follow-up examination showed an increase in cholesterol with increasing initial dioxin levels, as well as with increasing 1987 dioxin levels for those in earlier tours of duty. Ranch Hands in the high dioxin category had a greater average cholesterol level than Comparisons and Ranch Hands in the background dioxin category had a greater percentage of abnormally high cholesterol values than Comparisons.

Among moderate lifetime drinkers (no more than 40 drink-years at the time of the examination), Ranch Hands in the background dioxin category had a greater average cholesterol value at the 1992 follow-up examination than Comparisons. Among lifetime nondrinkers, Ranch Hands in the high dioxin category had a greater average cholesterol value than Comparisons. Among Ranch Hands who did not report exposure to degreasing chemicals, cholesterol values and the percentage of Ranch Hands with abnormally high cholesterol values increased with increasing initial dioxin levels.

Among heaviest current drinkers (more than four drinks per day) at the time of the 1992 follow-up examination, a greater percentage of Ranch Hands than Comparisons had abnormally high cholesterol values. Among the heaviest current drinkers, Ranch Hands in the background dioxin category had a greater percentage of abnormally high cholesterol values than Comparisons. Among moderate current drinkers (no more than four drinks per day), a greater percentage of Ranch Hands in the low dioxin category than Comparisons had abnormally high cholesterol values. Cholesterol levels and the percentage of abnormally high cholesterol levels for Ranch Hands and Ranch Hand officers at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

11.3.2. High-density Lipoprotein (HDL) Cholesterol

Among Ranch Hands who did not report exposure to degreasing chemicals, HDL cholesterol at the 1987 follow-up examination decreased with increasing initial dioxin and 1987 dioxin levels.

A greater percentage of Ranch Hands than Comparisons at the 1992 follow-up examination had abnormally low HDL cholesterol values. When looking at this increase by occupation Ranch Hand

officers had a greater percentage of abnormally low HDL relative to Comparison officers. Among the heaviest lifetime drinkers (more than 40 drink-years prior to the 1992 examination), a greater percentage of Ranch Hands in the background dioxin category than Comparisons had abnormally low HDL cholesterol values.

Among moderate lifetime drinkers (no more than 40 drink-years prior to the 1992 examination), HDL cholesterol values at the 1992 follow-up examination decreased and the percentage of Ranch Hands with abnormally low HDL cholesterol values increased with increasing 1987 dioxin levels. Similarly, HDL cholesterol values decreased as 1987 dioxin levels increased among Ranch Hands who were light or moderate drinkers (more than four drinks per day) at the time of the 1992 examination.

At the 1997 follow-up examination, a greater percentage of Ranch Hands in the background dioxin category than Comparisons had abnormally low HDL cholesterol values.

11.3.3. Cholesterol-HDL Ratio

Ranch Hands in the 1987 follow-up examination showed an increase in the cholesterol-HDL ratio with increasing initial dioxin levels. Ranch Hands in the high dioxin category had a greater average cholesterol-HDL ratio than Comparisons.

Ranch Hands with earlier tours of duty and those who did not report exposure to industrial chemicals showed an increase in cholesterol-HDL ratio at the 1987 follow-up examination. The percentage of Ranch Hands with an abnormally high cholesterol-HDL ratio value also increased as 1987 dioxin levels increased. In addition, the percentage of abnormally high cholesterol-HDL ratio values all Ranch Hands, Ranch Hands who did not report exposure to degreasing chemicals, and older Ranch Hands who did report exposure to degreasing chemicals, increased with increasing initial dioxin levels.

An increase in the cholesterol-HDL ratio, and an increase in the percentage of abnormally high cholesterol-HDL ratio values in Ranch Hands as 1987 dioxin levels increased, was observed at both the 1992 and 1997 follow-up examinations.

11.3.4. Triglycerides

Among the oldest participants in the 1985 follow-up examination, Ranch Hands had a greater average triglyceride value than Comparisons.

The 1987 follow-up examination showed that triglyceride values and the prevalence of abnormally high triglyceride values in Ranch Hands increased with increasing initial dioxin levels. Triglyceride values in Ranch Hands increased with increasing 1987 dioxin levels. The prevalence of abnormally high triglyceride values also increased with increasing 1987 dioxin levels in Ranch Hands with later tours of duty.

At the 1992 follow-up examination, Ranch Hand officers had a greater average triglyceride value and a greater percentage of abnormally high triglyceride values than Comparison officers did. An increase in the percentage of Ranch Hands with abnormally high triglyceride values was seen as 1987 dioxin levels increased. Ranch Hands in the high dioxin category had a greater average triglyceride value and a greater percentage of abnormally high triglyceride values than Comparisons. Among officers, triglyceride values increased with increasing initial dioxin levels. As 1987 dioxin levels increased in Ranch Hands as a group, and for officers who were moderate or heavy drinkers, an increase in triglyceride values was observed.

Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater occurrence of abnormally high triglyceride values than Comparison enlisted groundcrew. Ranch Hands in the high dioxin category had a greater average triglyceride value and a greater percentage of abnormally high

triglyceride values than Comparisons. In addition, as 1987 dioxin levels increased, triglyceride values and the prevalence of abnormally high triglyceride values in Ranch Hands increased.

The 2002 follow-up examination found that Ranch Hands had a greater occurrence of abnormally high triglyceride values than Comparisons. When looking by occupation, this result was found among Ranch Hand enlisted groundcrew. Similarly, Ranch Hands in the low and high dioxin categories had a greater occurrence of abnormally high triglyceride values than Comparisons. An increase in the prevalence of triglyceride abnormalities in Ranch Hands also was seen as 1987 dioxin levels increased.

11.4. LIVER DISORDERS, OTHER

A greater percentage of Ranch Hands in the high dioxin category than Comparisons had other liver disorders, based on data collected at the 1987 follow-up examination.

At the 1992 follow-up examination, other liver disorders among Ranch Hands increased with increasing initial and 1987 dioxin levels. Ranch Hands in the high dioxin category had a greater prevalence of other liver disorders than Comparisons.

The occurrence of other liver disorders increased with increasing initial dioxin levels, based on data collected at the 1997 follow-up examination. As in the 1987 and 1992 follow-up examinations, analysis of 1997 follow-up examination data found that Ranch Hands in the high dioxin category had a greater prevalence of other liver disorders than Comparisons.

A subsequent analysis of the 1997 follow-up examination was conducted to investigate whether the findings for the occurrence of other liver disorders could be explained by a particular subcategory of liver disorders (12). Five separate subcategories were explored. Although the associations described above were found when the five subcategories were combined, no associations were observed when the subcategories were analyzed individually.

11.5. LIVER ENZYMES

11.5.1. Alkaline Phosphatase

Analysis of 1985 follow-up examination data found that Ranch Hands had a greater average alkaline phosphatase value than Comparisons. Among those participants who did not report exposure to industrial chemicals, Ranch Hands also had a greater average alkaline phosphatase value than Comparisons.

Ranch Hands at the 1987 follow-up examination and Ranch Hands in the high dioxin category had a greater average alkaline phosphatase value than Comparisons. Black Ranch Hands also had a greater average alkaline phosphatase value than Black Comparisons. Alkaline phosphatase levels increased with increasing initial dioxin levels in Ranch Hands. In addition, the percentage of Ranch Hands with abnormally high alkaline phosphatase values increased with increasing 1987 dioxin among Ranch Hands with earlier tours of duty.

Among Ranch Hand participants, non-Black Ranch Hands, younger Ranch Hands, Ranch Hands who did report exposure to degreasing chemicals, and Ranch Hand enlisted groundcrew had a greater average alkaline phosphatase value at the 1992 follow-up examination. Among all participants and those who did not report exposure to degreasing chemicals, Ranch Hands in the background dioxin category and Ranch Hands in the low dioxin category had a greater average alkaline phosphatase value than Comparisons.

In addition, Ranch Hand enlisted groundcrew had a greater percentage of abnormally high alkaline phosphatase values than Comparison enlisted groundcrew at the 1992 follow-up examination. Similarly, Ranch Hands in the background dioxin category had a greater percentage of abnormally high alkaline

phosphatase values than Comparisons. Alkaline phosphatase levels increased with increasing 1987 dioxin levels among Black Ranch Hands.

The 1997 follow-up examination analysis found that for all participants and for enlisted groundcrew, Ranch Hands had a greater average alkaline phosphatase value than Comparisons. Ranch Hands in the background dioxin category also had a greater average alkaline phosphatase value than Comparisons.

Ranch Hand enlisted groundcrew at the 2002 follow-up examination had a greater percentage of abnormally high alkaline phosphatase values than Comparison enlisted groundcrew.

11.5.2. Alanine Aminotransferase (ALT)

Ranch Hands and younger Ranch Hands had increased ALT values at the 1987 follow-up examination with increasing initial dioxin levels. Among light alcohol drinkers (less than one drink per day) and Ranch Hands who did not report exposure to degreasing chemicals, the percentage of abnormally high ALT values increased with increasing initial dioxin levels. In addition, among lighter alcohol drinkers, ALT levels increased with increasing 1987 dioxin for Ranch Hands with earlier tours of duty. Ranch Hands in the high dioxin category had a greater average ALT value than Comparisons.

The analysis of ALT at the 1992 follow-up examination showed that ALT values in Ranch Hands and the percentage of Ranch Hands with abnormally high ALT values increased with increasing 1987 dioxin levels.

The 1997 follow-up examination analysis of ALT found that the percentage of Ranch Hands with abnormally high ALT values increased with increasing initial and 1987 dioxin levels. ALT values in Ranch Hands also increased with increasing 1987 dioxin levels. In addition, Ranch Hands in the low and high dioxin categories combined had a greater average ALT value than Comparisons.

11.5.3. Aspartate Aminotransferase (AST)

At the 1985 follow-up examination, among moderate alcohol drinkers (one to four drinks per day) Ranch Hands had a greater average AST value than Comparisons.

Among moderate drinkers at the time of the 1992 follow-up examination, AST values increased with increasing initial dioxin levels. Among heaviest drinkers (more than four drinks per day) at the time of the examination, AST values increased with increasing initial dioxin levels and 1987 dioxin levels.

The 1997 follow-up examination analysis showed that AST values and the percentage of abnormally high AST values increased with increasing 1987 dioxin. In addition, Ranch Hands in the high dioxin category had a greater average AST value than Comparisons.

11.5.4. Direct Bilirubin

Analysis of 1985 follow-up examination data found that, among participants who did not report exposure to industrial chemicals, a greater percentage of Ranch Hands than Comparisons had abnormally high direct bilirubin values.

Ranch Hands at the 1987 follow-up examination showed an increase in direct bilirubin values with increasing initial dioxin levels. In addition, Ranch Hands in the high dioxin category had a greater average direct bilirubin value than Comparisons.

11.5.5. Creatine Phosphokinase

Ranch Hands at the 1992 follow-up examination showed an increase in creatine phosphokinase values as 1987 dioxin levels increased. Similarly, the 1997 follow-up examination analysis showed an increase in

creatine phosphokinase values and an increase in the percentage of Ranch Hands with abnormally high creatine phosphokinase values as 1987 dioxin levels increased.

11.5.6. Gamma Glutamyltransferase (GGT)

GGT values at the 1987 follow-up examination increased with increasing initial dioxin levels. Similarly, the percentage of abnormally high GGT values increased with increasing initial dioxin levels for all Ranch Hands and specifically among Ranch Hands who did not report exposure to degreasing chemicals. Ranch Hands in both the low and high dioxin categories had a greater average GGT value and a greater prevalence of abnormally high GGT values than Comparisons. Among participants who did not report exposure to degreasing chemicals, a greater percentage of Ranch Hands in the high dioxin category than Comparisons had abnormally high GGT values. GGT values increased with increasing 1987 dioxin levels for Ranch Hands with later tours of duty.

Among Ranch Hands who did not report exposure to degreasing chemicals, GGT values at the 1992 follow-up examination increased with increasing initial dioxin. In addition, among participants who did not report exposure to degreasing chemicals, Ranch Hands in the high dioxin category had a greater average GGT value and a greater percentage of abnormally high GGT values than Comparisons. Ranch Hands, Ranch Hand officers and enlisted flyers showed an increase in GGT values as 1987 dioxin levels increased. The percentage of abnormally high GGT values increased with increasing 1987 dioxin levels.

The 1997 follow-up examination found that Ranch Hands in the high dioxin category had a greater average GGT value than Comparisons. GGT values and the percentage of abnormally high GGT values in Ranch Hands increased with increasing 1987 dioxin levels.

11.5.7. Lactate Dehydrogenase (LDH)

The 1992 follow-up examination analysis showed that, among enlisted groundcrew who were the heaviest lifetime drinkers (more than 40 drink-years), Ranch Hands had a greater average LDH value than Comparisons. Also among the heaviest lifetime drinkers, Ranch Hands in the background dioxin category had a greater percentage of abnormally high LDH values than Comparisons.

11.6. PROTEIN PROFILE

11.6.1. α-1-Acid Glycoprotein

At the 1992 follow-up examination among lifetime nondrinkers, Ranch Hands in the low dioxin category had a greater average α-1-acid glycoprotein value than Comparisons. In addition, younger Ranch Hands in the low dioxin category had a greater percentage of abnormally high α-1-acid glycoprotein values than younger Comparisons. Ranch Hand enlisted flyers had an increase in the percentage of abnormally high α-1-acid glycoprotein values at the 1992 follow-up examination as both initial dioxin and 1987 dioxin levels increased.

Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater average α-1-acid glycoprotein value than Comparison enlisted groundcrew.

11.6.2. α-1-Antitrypsin

Ranch Hands in the background dioxin category had a greater average α-1-antitrypsin value than Comparisons, as seen at the 1992 follow-up examination. In addition, α-1-antitrypsin values in Ranch Hands decreased with increasing 1987 dioxin levels.

Analysis of data from the 1997 follow-up examination revealed that Ranch Hands and Ranch Hand enlisted groundcrew had a greater average α-1-antitrypsin value than their Comparison counterparts.

Ranch Hands in both the background and high dioxin categories had a greater average α-1-antitrypsin value than Comparisons.

The 2002 follow-up examination analysis found that Ranch Hands in the low dioxin category had a greater percentage of abnormally high α-1-antitrypsin values than Comparisons.

11.6.3. α-2-Macroglobulin

Among older participants, α-2-macroglobulin values at the 1992 follow-up examination increased with increasing initial dioxin levels.

Ranch Hands at the 1997 follow-up examination showed an increase in the percentage of abnormally high α-2-macroglobulin values as 1987 dioxin levels increased.

11.6.4. Albumin

The 1992 follow-up examination of albumin found that among those who did not report exposure to industrial chemicals, Ranch Hands in the low dioxin category had a lower average albumin value than Comparisons. Among heaviest drinkers at the time of the 1992 examination and among participants who did not report exposure to degreasing chemicals, albumin decreased with increasing 1987 dioxin levels.

11.6.5. Apolipoprotein B

Among Ranch Hands and older Ranch Hands, both apolipoprotein B values and the percentage of abnormally high apolipoprotein B values at the 1992 follow-up examination increased with increasing initial dioxin levels and 1987 dioxin levels.

11.6.6. C3 Complement

The 1992 follow-up examination analysis of C3 complement found that Ranch Hands in the background dioxin category had a lower average C3 complement value than Comparisons.

11.6.7. C4 Complement

Ranch Hand officers at both the 1997 and 2002 follow-up examinations had a lower average C4 complement value than Comparison officers. In addition, analysis of 2002 follow-up examination data indicated that the average C4 complement value decreased and the percentage of abnormally low C4 complement values increased with increasing initial dioxin.

11.6.8. Haptoglobin

For all participants and, specifically, among enlisted groundcrew, Ranch Hands had a greater average haptoglobin value than Comparisons at the 1992 follow-up examination. Among Ranch Hand officers, the percentage of abnormally high haptoglobin values increased with increasing initial dioxin levels.

Ranch Hands and Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater average haptoglobin value than Comparisons. The percentage of abnormally high haptoglobin values was also greater for Ranch Hands than for Comparisons. Ranch Hands in the background dioxin category had a greater average haptoglobin value and a greater percentage of abnormally high haptoglobin values than Comparisons. In addition, Ranch Hands in the low and high dioxin categories combined had a greater average haptoglobin value than Comparisons.

As in the 1997 follow-up examination, Ranch Hands and Ranch Hand enlisted groundcrew in the 2002 follow-up examination had a greater average haptoglobin value than Comparisons.

11.6.9. Prealbumin

Among participants who did not report exposure to degreasing chemicals, prealbumin values at the 1992 follow-up examination decreased with increasing 1987 dioxin levels.

Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater percentage of abnormally low prealbumin values than Comparison enlisted groundcrew. Similarly, Ranch Hands in the high dioxin category had a greater percentage of abnormally low prealbumin values than Comparisons.

11.7. PROTHROMBIN TIME

The 1987 follow-up examination of prothrombin time revealed an increase in prothrombin time as initial dioxin levels increased among Ranch Hands, and, in particular, among Ranch Hands who were moderate lifetime smokers (no more than 10 pack-years). In addition, the 1987 follow-up examination found Ranch Hands with later tours of duty had an increased prevalence of prothrombin time abnormalities as 1987 dioxin levels increased.

As in the 1987 follow-up examination, the 1992 follow-up examination showed an increase in prothrombin time with increasing initial dioxin levels among Ranch Hands.

Ranch Hands in the background dioxin category had a higher average prothrombin time than Comparisons at the 2002 follow-up examination.

11.8. SKIN BRUISES, PATCHES, OR SENSITIVITY

The 1987 follow-up examination found that Ranch Hands in each of the background, low and high dioxin categories had a greater occurrence of self-reported skin bruises, patches, or sensitivity than Comparisons.

11.9. STOOL HEMOCCULT

The 1992 follow-up examination showed that among the heaviest lifetime drinkers, a greater percentage of Ranch Hands than Comparisons had positive stool hemoccult results. This was also seen in the Ranch Hand officers and enlisted groundcrew when analyzed by occupation. A greater percentage of Ranch Hands in the low dioxin category than Comparisons also had positive stool hemoccult results.

A greater percentage of Ranch Hand officers than Comparison officers had positive stool hemoccult results at the 2002 follow-up examination.

11.10. ARTICLE

11.10.1. Dioxin and Hepatic Abnormalities in Veterans of Operation Ranch Hand

The serum dioxin level in relation to the prevalence of liver disease and hepatomegaly through March 1993 of participants at either the 1982, 1985, 1987 or 1992 physical examination and in relation to the results of the liver function tests [ALT, AST, GGT, LDH, alkaline phosphatase, and total bilirubin] measured on those that attended only the 1992 physical examination were analyzed in a journal article appearing in the *Annals of Epidemiology* in 2001 (8). The analysis for history of liver disease was adjusted for birth year, race, military occupation, lifetime industrial chemical exposure, lifetime degreasing chemical exposure, lifetime drinking history, and lifetime smoking history. In addition, when analyzing liver function tests, adjustments were also made for current alcohol use and current smoking. Ranch Hands with the highest dioxin levels had an increased risk of "other liver disorders," primarily due to increased transaminases (AST, ALT) or LDH and to other nonspecific liver abnormalities. The GGT

mean level increased with dioxin in the Ranch Hand group and the mean in the high category was increased. The increased GGT levels may have been due to confounding or reverse causality, thus, there was no strong evidence of dioxin or herbicide-induced liver disease.

11.11. CONCLUSION

Although numerous statistically significant findings were listed, many were just in isolated subpopulations, values were increased in one exam and not elevated in another, and findings rarely occurred in the same group in different examinations. An article that looked at the associations between hepatic abnormalities and liver function tests and dioxin through 1992 examination found in the Ranch Hand with the highest dioxin levels an increase in "other liver disorders". Analysis of the individual diagnoses that comprised "other liver disorders" showed the increase was primarily due to increased ALT, LDH, and other nonspecific abnormalities. However, LDH was not elevated at the 1997 and 2002 follow-up examinations and ALT although increased with dioxin in 1997 was not increased in 2002. Furthermore, the gastrointestinal data reflected no apparent increase in organ-specific morbidity, nor did they reflect an association with dioxin. However, throughout the AFHS triglycerides had shown elevated values in association with dioxin; therefore, a subclinical dioxin effect on lipid metabolism could not be excluded.

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12. HEMATOLOGY ASSESSMENT

12.1. INTRODUCTION

Hematology is the study of red blood cells, white blood cells, platelets, and plasma, components that perform important functions related to fighting infections, regulating temperature, transporting oxygen to other cells, and the balancing of body fluids. Scientific literature has not identified any consistent relation between exposure to Agent Orange or dioxin and hematopoietic toxicity to date. The AFHS examined the basic components of the participants' blood at each of the six physical examinations (1-7).

A complete blood count was performed at the 1982, 1985, 1987, 1992, 1997, and 2002 AFHS examinations. Elements of the complete blood count that were analyzed were hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, and white blood cell (WBC) count. Analysis also was performed on mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume for the 1982, 1985, and 1987 examinations. In addition, erythrocyte sedimentation rate was analyzed at all six examinations.

Analysis of a differential WBC count was performed for the 1992, 1997, and 2002 follow-up examinations, with the differential results reported as absolute counts. The absolute WBC counts of segmented neutrophils, neutrophilic bands, lymphocytes, monocytes, eosinophils, and basophils were analyzed. Lymphocytes included both reactive and nonreactive lymphocytes. Also at these examinations, RBC morphology was constructed from a number of laboratory findings such as rouleaux, Burr cells, anisocytosis, and Howell-Jolly bodies, many of which were few in numbers.

Fibrinogen measurements were collected and analyzed for the 2002 follow-up examination.

AFHS staff and their colleagues wrote the following journal article:

- Relation of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) level to hematological examination results in veterans of Operation Ranch Hand (8).

The IOM Veterans and Agent Orange reports through 2004 did not address non-cancerous hematological disorders.

The following chart lists the variables that were analyzed for the hematology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Basophils, Absolute					**X**	X	X
Eosinophils, Absolute					X	X	X
Erythrocyte Sedimentation Rate	X	**X**	**X**	**X**	**X**	**X**	**X**
Fibrinogen							X
Hematocrit	X	X	X	**X**	X	X	X
Hemoglobin	X	X	X	**X**	X	X	X
Lymphocytes, Absolute					X	X	X
Mean Corpuscular Hemoglobin	**X**	X	X	X			

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Mean Corpuscular Hemoglobin Concentration	X	X	X	**X**			
Mean Corpuscular Volume	**X**	X	X	**X**			
Monocytes, Absolute					X	X	X
Neutrophils, Absolute (bands)					X	**X**	X
Neutrophils, Absolute (segs)					**X**	X	X
Platelet Count	X	**X**	**X**	**X**	**X**	**X**	**X**
RBC Count	X	X	X	**X**	**X**	X	X
RBC Morphology					**X**	X	**X**
WBC Count	X	**X**	X	**X**	**X**	X	**X**

12.2. BASOPHILS, ABSOLUTE

At the 1992 follow-up examination, absolute basophil counts increased with increasing levels of 1987 dioxin among Black Ranch Hands.

12.3. ERYTHROCYTE SEDIMENTATION RATE

Ranch Hands at the 1985 follow-up examination had a greater prevalence of elevated erythrocyte sedimentation rates than Comparisons.

The 1987 follow-up examination analyses found that Ranch Hands in the high dioxin category had a greater average erythrocyte sedimentation rate than Comparisons. This result was observed when all Ranch Hands were examined, as well as when the analysis was restricted to older Ranch Hands and Comparisons. Younger Ranch Hands in the low dioxin category had a greater average erythrocyte sedimentation rate than younger Comparisons. Similarly, Ranch Hands had a greater percentage of elevated erythrocyte sedimentation rates than Comparisons; this pattern also was seen when Ranch Hands were categorized by both low dioxin levels and high dioxin levels. Erythrocyte sedimentation rates and the prevalence of elevated erythrocyte sedimentation rates increased in Ranch Hands as initial dioxin levels increased and as 1987 dioxin levels increased.

Erythrocyte sedimentation rates at the 1992 and 1997 follow-up examinations increased with increasing 1987 dioxin levels. The percentage of elevated erythrocyte sedimentation rates observed at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

Ranch Hands in the low and high dioxin categories combined had a greater average erythrocyte sedimentation rate than Comparisons at the 2002 follow-up examination.

12.4. HEMATOCRIT

Ranch Hands with later tours of duty showed increased hematocrit values at the 1987 follow-up examination as 1987 dioxin increased.

12.5. HEMOGLOBIN

Analysis of 1987 follow-up examination data found that hemoglobin values for Ranch Hands with later tours of duty increased with increasing 1987 dioxin.

12.6. MEAN CORPUSCULAR HEMOGLOBIN

At the 1982 baseline examination, Ranch Hands had a higher average mean corpuscular hemoglobin than Comparisons.

12.7. MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION

At the 1987 follow-up examination, Ranch Hands in the background and low dioxin categories had a higher average mean corpuscular hemoglobin concentration than Comparisons.

12.8. MEAN CORPUSCULAR VOLUME

Ranch Hands had a greater mean corpuscular volume than Comparisons at the 1982 baseline examination. At the 1987 follow-up examination, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high mean corpuscular volume levels than Comparisons. In addition, the 1987 follow-up examination found that among the heaviest lifetime smokers (>10 pack-years), the prevalence of mean corpuscular volume abnormalities increased with increasing initial dioxin levels.

12.9. NEUTROPHILS, ABSOLUTE (bands)

At the 1997 follow-up examination, Ranch Hands in the low and high dioxin categories combined, had a higher average absolute neutrophil (band) count than Comparisons.

12.10. NEUTROPHILS, ABSOLUTE (segs)

Absolute neutrophil counts (segs) increased among Black Ranch Hand participants and among officers with increasing initial dioxin levels at the 1992 follow-up examination. In addition, the 1992 follow-up examination analysis detected increased absolute neutrophil counts (segs) as 1987 dioxin levels increased among Black Ranch Hands.

12.11. PLATELET COUNT

For heavy smokers at the 1985 follow-up examination, Ranch Hands had a greater average platelet count than Comparisons.

Analysis performed for the 1987 follow-up examination showed that Ranch Hands had a greater average platelet count and a greater occurrence of abnormally high platelet counts than Comparisons. The differences were primarily in younger Ranch Hands and Ranch Hands in the high dioxin category.

Enlisted Ranch Hands had a greater average platelet count at the 1992 follow-up examination than Comparisons. In addition, Ranch Hands in the high dioxin category had a greater average platelet count and a greater prevalence of abnormally high platelet counts than Comparisons. The 1992 follow-up examination also found that the occurrence of abnormally high platelet counts increased with increasing 1987 dioxin levels.

The 1997 follow-up examination found Ranch Hands in the high dioxin category had a greater average platelet count than Comparisons. The average platelet count was greater among Ranch Hand enlisted personnel than Comparison enlisted personnel. The average platelet count was lower among Ranch Hand officers than Comparison officers. Ranch Hand officers also had a higher prevalence of abnormally low platelet counts than Comparison officers did.

Ranch Hand enlisted flyers had a greater average platelet count than Comparison enlisted flyers at the 2002 follow-up examination.

12.12. RBC COUNT

Analyses of RBC count performed for the 1987 follow-up examination found that among older participants with earlier tours of duty, RBC counts decreased with increasing 1987 dioxin levels. Among younger participants with earlier tours of duty, however, RBC counts increased with increasing 1987 dioxin levels. In addition, for Ranch Hands with earlier tours of duty, the prevalence of abnormally low RBC counts increased with increasing 1987 dioxin levels.

The 1992 follow-up examination found that among the heaviest smoking officers (more than 20 cigarettes per day), Ranch Hands had a greater average RBC count than Comparisons. This difference was due primarily to heavy Ranch Hand smokers in the background dioxin category.

12.13. RBC MORPHOLOGY

The 1992 follow-up examination revealed an increase in the occurrence of abnormal RBC morphology results as 1987 dioxin levels increased.

Ranch Hand enlisted groundcrew at the 2002 follow-up examination had a greater prevalence of RBC morphology abnormalities than Comparison enlisted groundcrew. In addition, Ranch Hands in the high dioxin category had a greater occurrence of RBC morphology abnormalities than Comparisons.

12.14. WBC COUNT

At the 1985 follow-up examination younger Black officer and enlisted flyer Ranch Hands had lower average WBC counts than their Comparison counterparts did. Younger non-Black heavy-smoking Ranch Hands had a greater average WBC count than younger non-Black heavy-smoking Comparisons.

At the 1987 follow-up examination, Ranch Hands in the high dioxin category also had a greater average WBC count than Comparisons. In addition, WBC counts increased with increasing 1987 dioxin levels. Among younger participants with earlier tours of duty, WBC counts also increased with increasing 1987 dioxin levels.

At the 1992 follow-up examination, Ranch Hands had lower average WBC counts than Comparisons among Black participants and officers. However, among Black participants and among officers, WBC counts increased with increasing initial dioxin levels. Similarly, WBC counts increased with increasing 1987 dioxin levels among Black participants.

WBC counts decreased with increasing 1987 dioxin levels based on the evaluation of 2002 follow-up examination data.

12.15. ARTICLE

12.15.1. Relation of Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) Level to Hematological Examination Results in Veterans of Operation Ranch Hand

A journal article published in 2001 (8) provided results of a study of indices of hematological function at the 1982, 1985, 1987 or 1992 AFHS examinations and their relations to dioxin and herbicides. The indices of hematological function studied were RBC count, hemoglobin, hematocrit, WBC count, platelets, mean corpuscular volume and erythrocyte sedimentation rate. No consistent relationship between dioxin body burden and RBC count, hemoglobin, hematocrit, WBC count and erythrocyte

sedimentation rate was found. Mean corpuscular volume and platelet count, however, generally increased with increasing dioxin level at each of the four examinations. Compared to veterans not involved with the spraying of herbicides, those with the highest dioxin levels in the Ranch Hand had mean corpuscular volumes that were about 1% higher and platelet counts that were about 4% higher. These small increases were unlikely to be of clinical significance and the data could not determine if these associations resulted from dioxin exposure.

12.16. CONCLUSION

The article that studied hematological functions covering 1982, 1985, 1987, and 1992 AFHS examinations found a generally consistent relation of increased mean corpuscular volume and platelet counts with increasing dioxin levels. No consistent relationship between dioxin and RBC count, hemoglobin, hematocrit, WBC count or erythrocyte sedimentation rate was found. The magnitude of increase was only 1% for mean corpuscular volume and 4% for platelet count between the lowest and highest dioxin levels. The 1997 and 2002 examinations did not study mean corpuscular volume. However, platelet counts continued to show an increase in the high dioxin group in the 1997 examination. However, these findings were not seen in the 2002 examination. Thus, the small increases were unlikely to be of clinical significance, and appeared to have declined in the last examination and may not have been caused by dioxin.

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13. IMMUNOLOGY ASSESSMENT

13.1. INTRODUCTION

Overt damage to organs of the immune system and depressed immunologic function has been noted in a variety of animals exposed to dioxin. As the fields of immunology and immunotoxicology have grown in the past 25 years, a significant spectrum of subtle immunotoxic effects has been described in animals, but for many possible reasons comparable adverse effects have not been recorded consistently in exposed humans.

Data from the physical examination (composite skin test measurements at the 1987 and 1992 follow-up examinations, as described below) and the immunology laboratory were used to assess the immunological function for the 1982, 1985, 1987, 1992, 1997, and 2002 AFHS examinations (1-7). At the physical examinations, not all participants had all immunology laboratory tests performed; immunologic cell function and phenotyping were usually limited due to cost and test complexity. The percentage of randomly selected participants who had the tests accomplished ranged from 26% to 67%.

Human leukocyte antigen-DR (HLA-DR) was analyzed at the 1985 and 1987 follow-up examinations.

Immunoglobulins measure the ability of a specific B-cell subgroup to secrete a specific antibody. The antibodies typically rise in response to infections or immunizations with bacteria, fungi, and viruses. Analyses were performed on immunoglobulin (Ig) A, IgG, and IgM for 1987, 1992, 1997, and 2002 follow-up examinations.

Lupus panel tests were performed for the 1992, 1997, and 2002 follow-up examinations. These tests detected the most common autoantibodies found in humans. Autoantibodies are markers for autoimmune diseases, and the lupus panel is considered a screening assay for a wide spectrum of autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). Occasionally, autoantibodies are detected in asymptomatic persons; this is alternatively explained as evidence for incipient autoimmune disease or a finding of unknown meaning. The lupus panel, based on the manual indirect fluorescent antibody method, comprised the following individual tests on serum:

- Antinuclear antibody (ANA)
- Thyroid microsomal antibody
- Mouse stomach kidney (MSK) section stain for the following specific autoantibodies:
    - Anti-smooth muscle
    - Anti-mitochondrial
    - Anti-parietal cell
- Rheumatoid factor.

The lupus panel at the 1992 follow-up examination also included B-cell clones detected by serum protein electrophoresis, other antibodies and a summary index.

Absolute lymphocyte measures the absolute number of total lymphocytes circulating in peripheral blood. Absolute lymphocytes were analyzed at all AFHS physical examinations except for 1985. For the 1982, 1987 and 1992 physical examinations, this measurement was referred to as total lymphocyte count. Lymphocytes recognize and destroy bacteria, fungi, viruses, and other foreign bodies.

Responses to stimulation by pokeweed mitogen (PWM) were analyzed for the 1985 follow-up examination. The PWM study measured the functional capability of T cells to become activated by mitogen and undergo proliferations.

Cell function responses to stimulation by phytohemagglutinin (PHA), mixed lymphocyte culture (MLC), and two natural killer cell assays were analyzed for the 1985 and 1987 follow-up examinations. The PHA studies measured the functional capability of T-cells to become activated by mitogen and undergo proliferation. The MLC studies measured the reactivity of T cells to foreign histocompatibility class II antigens. The natural killer cells studies measured natural killer cell activity both without Interleukin-2 (NKCA) and with Interleukin-2 (NKCI).

For the 1987 and 1992 follow-up examinations, a composite skin test was constructed based on the responses to four separate antigens – *Candida albicans*, mumps, Trichophyton, and staph-phage lysate. The antigens were injected intradermally and a positive response to any of the four indicated intact cell-mediated immunity. The skin test was considered abnormal if none of the four antigen responses was positive.

Cell surface marker measurements were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of the tests. Quantification of the different cell populations was carried out with the use of reagent mouse monoclonal antibodies. CD4+ cells (helper T cells), CD8+ cells (suppressor cells), and CD20+ cells (B cells) were analyzed for all six AFHS examinations. The cell surface marker measurements of CD2+ cells, CD3+ cells, CD5+ cells, CD14+ cells, CD16+56+ cells, CD25+ cells, and human leukocyte antigen-DR (HLA-DR) cells were analyzed at one or more of the AFHS examinations. Analysis of double-labeled cells (cells that express two markers) were done for CD3- with CD16+56+, CD3+ with CD25+, CD4+ with CD8+, and CD5+ with CD20+ at the 1992 follow-up examination, and CD3+CD4+ at the 1997 and 2002 follow-up examinations.

The following journal article was written by AFHS staff and their colleagues:

- Serum dioxin and immunologic response in veterans of Operation Ranch Hand (8).

In 2002, a Committee for the IOM found that the evidence determining whether an association exists between Agent Orange and other herbicides used in Vietnam and immune suppression or autoimmunity was inadequate or insufficient (9). This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (10).

The following chart lists the variables that were analyzed for the immunology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
CD2+ Cells (Total T Cells)	X	**X**	X	**X**			
CD3+ Cells (Total T Cells)	X				**X**	**X**	X
CD4+ Cells (Helper T Cells)	X	X	X	**X**	**X**	**X**	X
CD4+:CD8+ Ratio	X	X	X	X	**X**		
CD5+ Cells (T-cell Marker)					**X**		
CD8+ Cells (Suppressor Cells)	X	X	X	**X**	**X**	X	X
CD14+ Cells (Monocytes)		**X**	X	**X**	**X**		
CD16+56+ Cells (Natural Killer Cells)			X	**X**	X	**X**	X
CD20+ Cells (B Cells)	X	**X**	X	**X**	**X**	X	**X**

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
CD25+ Cells (Activation Marker for Lymphocytes)			X	**X**	**X**		
Double-Labeled Cells: CD3- with CD16+56+					**X**		
Double-Labeled Cells: CD3+ with CD25+					**X**		
Double-Labeled Cells: CD3+CD4+ Cells (Helper T Cells)						**X**	X
Double-Labeled Cells: CD4+ with CD8+					**X**		
Double-Labeled Cells: CD5+ with CD20+					**X**		
HLA-DR Cells		X	X	**X**			
Immunoglobulins: IgA			X	**X**	**X**	**X**	X
Immunoglobulins: IgG			X	**X**	**X**	X	X
Immunoglobulins: IgM			X	**X**	**X**	X	**X**
Lupus Panel: ANA Test					X	X	**X**
Lupus Panel: Thyroid Microsomal Antibody					**X**	X	X
Lupus Panel: B-Cell Clones Detected by Serum Protein Electrophoresis					X		
Lupus Panel: MSK Anti-Mitochondrial Antibody					X	X	X
Lupus Panel: MSK Anti-Parietal Antibody					X	X	X
Lupus Panel: MSK Anti-Smooth Muscle Antibody					X	X	**X**
Lupus Panel: Other Antibodies					X		
Lupus Panel: Rheumatoid Factor					**X**	X	**X**
Lupus Panel: Summary Index					X		
Lymphocytes, Absolute	X		X	**X**	**X**	X	X
MLC: Net Response			X	X			
MLC: Unstimulated Response			X	**X**			
NKCA 50/1: Net Response			X	X			
NKCA 50/1: Percent Release			**X**	X			
NKCI 50/1: Net Response			**X**	**X**			
NKCI 50/1: Percent Release			**X**	**X**			
PHA: Maximum Net Response			X	**X**			
PHA: Net Response			**X**	**X**			
PHA: Unstimulated Response			X	X			
PWM: Pokeweed Mitogen Net Response		X					
Skin Test Diagnosis, Composite			**X**	X	**X**		

13.2. CD2+ CELLS (TOTAL T CELLS)

The 1985 follow-up examination found that Black Ranch Hands had a lower average CD2+ cell count than Black Comparisons.

Among participants who drank more than one drink per day, CD2+ cell counts at the 1987 follow-up examination decreased with increasing levels of initial dioxin. In addition, younger Ranch Hands in the background dioxin category who were moderate lifetime drinkers (no more than 40 drink-years) had a lower average CD2+ cell count than younger Comparisons who were moderate lifetime drinkers.

13.3. CD3+ CELLS (TOTAL T CELLS)

Ranch Hand officers in the high dioxin category had a greater average CD3+ cell count than Comparisons at the 1992 follow-up examination.

Analysis of data collected for the 1997 follow-up examination showed that CD3+ cell counts in Ranch Hands increased with increasing 1987 dioxin levels.

13.4. CD4+ CELLS (HELPER T CELLS)

Among Ranch Hands who were moderate lifetime drinkers (no more than 40 drink-years) with later tours of duty who participated in the 1987 follow-up examination, CD4+ cell counts decreased as 1987 dioxin levels increased.

Analysis of CD4+ cells for the 1992 follow-up examination found that Ranch Hand officers in the high dioxin category had a greater average CD4+ cell count than Comparison officers.

CD4+ cell counts in Ranch Hands at the 1997 follow-up examination increased with increasing 1987 dioxin levels.

13.5. CD4+:CD8+ RATIO

The 1992 follow-up examination analysis of the ratio of CD4+ cells to CD8+ cells found that among participants with moderate physical activity, Ranch Hands had a greater average ratio than Comparisons.

13.6. CD5+ CELLS (T-CELL MARKER)

Analysis of CD5+ cells for the 1992 follow-up examination showed Ranch Hand officers in the high dioxin category had a greater average CD5+ cell count than Comparison officers.

13.7. CD8+ CELLS (SUPPRESSOR CELLS)

Among the heaviest drinkers (current and lifetime) at the 1987 follow-up examination, CD8+ cell counts decreased with increasing levels of initial dioxin.

Among officers, CD8+ cell counts increased at the 1992 follow-up examination with initial dioxin levels. In addition, the categorized dioxin analysis showed that among officers, Ranch Hands in the high dioxin category had a greater average CD8+ cell count than Comparisons. Ranch Hand enlisted flyers in the high dioxin category had a lower average CD8+ cell count than Comparison enlisted flyers. Ranch Hand enlisted groundcrew in the background dioxin category had a greater average CD8+ cell count than Comparison enlisted groundcrew.

13.8. CD14+ CELLS (MONOCYTES)

Analysis of CD14+ cells at the 1985 follow-up examination showed that among enlisted groundcrew who were currently drinking more than four drinks per day, Ranch Hands had a greater average CD14+ cell count than Comparisons.

Among the heaviest lifetime smokers (more than 10 pack-years) at the time of the 1987 follow-up examination with earlier tours of duty, CD14+ cell counts increased with increasing 1987 dioxin levels.

The 1992 follow-up examination analysis of CD14+ cells found Ranch Hand enlisted flyers had a lower average CD14+ cell count than Comparison enlisted flyers. In addition, older Ranch Hands in the low dioxin category had lower average CD14+ cell counts than older Comparisons.

13.9. CD16+56+ CELLS (NATURAL KILLER CELLS)

At the 1987 follow-up examination, Ranch Hand officers showed an increase in CD16+56+ counts with increasing initial dioxin levels. In addition, among officers and lifetime nondrinkers, Ranch Hands in the high dioxin category had a greater average CD16+56+ cell count than Comparisons. A lower average CD16+56+ cell count was seen among Ranch Hands in the low dioxin category who were moderate lifetime drinkers or who were moderately active than among Comparisons. Ranch Hand enlisted flyers in the high dioxin category and Ranch Hand officers in the low dioxin category had lower average CD16+56+ cell counts than Comparison enlisted flyers and Comparison officers, respectively.

Among enlisted flyers at the 1997 follow-up examination, Ranch Hands had a lower average CD16+56+ cell count than Comparisons. Similarly, Ranch Hands in the high dioxin category had a lower average CD16+56+ cell count than Comparisons.

13.10. CD20+ CELLS (B CELLS)

The 1985 follow-up examination of CD20+ cells revealed that among non-Black participants who never smoked, Ranch Hands had a lower average CD20+ cell count than Comparisons.

Among older Ranch Hands who participated in the 1987 follow-up examination, CD20+ cell counts increased as initial dioxin levels increased. Also, among older participants, Ranch Hands in the background dioxin category, as well as Ranch Hands in the high dioxin category, had greater average CD20+ cell counts than Comparisons. Analysis of 1987 follow-up examination data also showed that among Ranch Hands with earlier tours of duty, CD20+ cell counts increased with increasing 1987 dioxin levels.

The analysis of CD20+ cells at the 1992 follow-up examination found that Ranch Hands in the background dioxin category had greater average CD20+ cell counts than Comparisons.

An increase in CD20+ cells counts in Ranch Hands was seen at the 2002 follow-up examination as initial dioxin levels increased.

13.11. CD25+ CELLS (ACTIVATION MARKER FOR LYMPHOCYTES)

At the 1987 follow-up examination, Ranch Hands who were current cigarette smokers, light lifetime smokers and light lifetime drinkers had increased CD25+ cell counts with increasing initial dioxin levels. CD25+ cell counts decreased with increasing 1987 dioxin levels for Ranch Hands with later tours of duty.

The analysis of CD25+ cells at the 1992 follow-up examination showed that among enlisted flyers, Ranch Hands had a lower average CD25+ cell count than Comparisons. Ranch Hand enlisted flyers in the low and high dioxin categories combined had a lower average CD25+ cell count than Comparison enlisted flyers. Ranch Hand officers in the high dioxin category had a greater average CD25+ cell count than Comparison officers. In addition, among participants who did not drink, Ranch Hands in the high dioxin category had greater average CD25+ cell counts than Comparisons.

13.12. DOUBLE-LABELED CELLS

13.12.1. CD3- with CD16+56+

Analysis for the 1992 follow-up examination found that the number of cells that expressed CD3- and CD16+56+ markers decreased with increasing 1987 dioxin levels.

13.12.2. CD3+ with CD25+

Among enlisted flyers at the 1992 follow-up examination, Ranch Hands and in particular, Ranch Hands in the low and high dioxin categories combined had a lower average CD3+ with CD25+ cell count than Comparisons. Among lifetime nondrinkers and among officers, Ranch Hands who were in the high dioxin category had a higher average CD3+ with CD25+ cell count than Comparisons.

13.12.3. CD3+CD4+ Cells (Helper T Cells)

The analysis for the 1997 follow-up examination revealed an increase in CD3+CD4+ cell counts in Ranch Hands as 1987 dioxin levels increased.

13.12.4. CD4+ with CD8+

Among Blacks and officers at the 1992 follow-up examination, Ranch Hands in the background dioxin category had a lower average CD4+ with CD8+ cell count than their Comparison counterparts. In addition, older Ranch Hands in the low dioxin category had a lower average CD4+ with CD8+ cell count than older Comparisons. Ranch Hand enlisted groundcrew in the background dioxin category had a higher average CD4+ with CD8+ cell count than Comparison enlisted groundcrew.

13.12.5. CD5+ with CD20+

Analysis of 1992 follow-up examination data showed that the number of cells that express both CD5+ and CD20+ markers increased with increasing 1987 dioxin levels.

13.13. HUMAN LEUKOCYTE ANTIGEN (HLA)-DR CELLS

Among younger Ranch Hands who participated in the 1987 follow-up examination, HLA-DR counts decreased as initial dioxin levels increased. Among older participants, and, in particular, among older participants who currently drank no more than one drink per day, HLA-DR counts increased with increasing initial dioxin levels. In addition, among older participants, Ranch Hands in the high dioxin category had a greater average HLA-DR count than Comparisons.

13.14. IMMUNOGLOBULINS

13.14.1. IgA

At the 1987 follow-up examination, among Ranch Hands with earlier tours of duty who used to smoke but quit, IgA values increased with increasing 1987 dioxin levels. Ranch Hands in the background dioxin category had a lower average IgA value than Comparisons.

IgA values in Ranch Hands at both the 1987 and 1997 follow-up examinations increased with increasing initial dioxin levels.

Among Black participants at the 1992 follow-up examination, Ranch Hands in the low dioxin category had a greater average IgA value than Comparisons.

13.14.2. IgG

At the 1987 follow-up examination, Ranch Hands in the background dioxin category had a lower average IgG value than Comparisons. At the 1992 follow-up examination, Ranch Hand officers in the high dioxin category had a lower average IgG value than Comparison officers.

13.14.3. IgM

At the 1987 follow-up examination, among Ranch Hands who were moderate current drinkers (between one and four drinks per day) IgM values decreased with increasing initial dioxin levels. Also, among Ranch Hands with later tours of duty, IgM values decreased with increasing 1987 dioxin levels.

Based on data from the 1992 follow-up examination, Black Ranch Hands had a lower average IgM value than Black Comparisons. Similarly, among sedentary participants, Ranch Hands had a lower average IgM value than their Comparison counterparts did. This was also true for sedentary Ranch Hand enlisted flyers. Very active Ranch Hands and very active Ranch Hands in the low dioxin category however, had a greater average IgM value than Comparisons.

Ranch Hand enlisted flyers at the 2002 follow-up examination had a lower average IgM value than Comparison enlisted flyers.

13.15. LUPUS PANEL

13.15.1. Antinuclear Antibody (ANA) Test

At the 2002 follow-up examination, the presence of ANA increased with increasing initial dioxin levels.

13.15.2. ANA Thyroid Microsomal Antibody

Among heaviest lifetime drinkers (more than 40 drink-years at the time of the examination) and among all minimal current drinkers (no more than one drink per day), a greater percentage of Ranch Hands than Comparisons had ANA thyroid microsomal antibodies present at the 1992 follow-up examination.

Among participants who were currently smoking cigarettes at the time of the 1992 follow-up examination, a greater percentage of Ranch Hands in each of the background, low, and high dioxin categories than Comparisons had ANA thyroid microsomal antibodies present. Among former smokers and the heaviest lifetime drinkers, Ranch Hands in the low dioxin and in the high dioxin categories each had a greater prevalence of ANA thyroid microsomal antibodies present than Comparisons. Among minimal current drinkers, a greater percentage of Ranch Hands in the low dioxin category than Comparisons had ANA thyroid microsomal antibodies present.

13.15.3. Mouse Stomach Kidney (MSK) Anti-smooth Muscle Antibody

The 2002 follow-up examination found that Ranch Hand officers had a greater presence of anti-smooth muscle antibodies than Comparison officers. In addition, a greater percentage of Ranch Hands in the background dioxin category had anti-smooth muscle antibodies present than Comparisons.

13.16. RHEUMATOID FACTOR

Among Ranch Hand enlisted groundcrew who participated in the 1992 follow-up examination, the occurrence of a positive rheumatoid factor increased with initial dioxin levels. In addition, among Ranch Hands in the background dioxin category, enlisted groundcrew and moderately physically active participants had a greater presence of positive rheumatoid factor results than their Comparison counterparts did.

A greater percentage of Ranch Hand officers at the 2002 follow-up examination had a positive rheumatoid factor than Comparison officers did. In addition, Ranch Hands in the low dioxin category had a higher prevalence of positive rheumatoid factor results than Comparisons.

13.17. LYMPHOCYTES, ABSOLUTE

At the 1987 follow-up examination, among Ranch Hands who drank more than one drink per day, absolute lymphocytes decreased as initial dioxin levels increased. Among younger participants who were moderate lifetime drinkers (less than 40 drink-years at the time of the examination), Ranch Hands in the background dioxin category had a lower average absolute lymphocyte count than Comparisons. In addition, younger Ranch Hands in the high dioxin category who were lifetime nondrinkers had a lower average absolute lymphocyte count than their Comparison counterparts.

The 1992 follow-up examination found that among moderately active Ranch Hands, absolute lymphocytes increased with increasing initial dioxin levels.

13.18. MIXED LYMPHOCYTE CULTURE (MLC), UNSTIMULATED RESPONSE

Analysis of data from the 1987 follow-up examination showed that Ranch Hands in the high dioxin category had a greater average unstimulated MLC response than Comparisons. In addition, among Ranch Hands who were lifetime nonsmokers and had earlier tours of duty, unstimulated MLC values increased as 1987 dioxin levels increased.

13.19. NATURAL KILLER CELLS

13.19.1. Natural Killer Cell Assay (NKCA) 50/1 Percent Release

Analysis of data from the 1987 follow-up examination found that Black Ranch Hands had a greater average NCKA 50/1 percent release than Black Comparisons.

13.19.2. Natural Killer Cell Assay with Interleukin-2 (NKCI) 50/1 Percent Release and Net Response

Black Ranch Hands in the 1987 follow-up examination had a greater average NKCI percent release than Black Comparisons. Among non-Black participants who were the heaviest drinkers, Ranch Hands in the low dioxin category had a greater average NKCI percent release than Comparisons. In addition, among non-Black participants with later tours of duty and among Black participants with earlier tours of duty, NKCI percent release values increased with increasing levels of 1987 dioxin.

The same results were seen for NKCI 50/1 net response at the 1987 follow-up examination.

13.20. PHYTOHEMAGGLUTININ (PHA)

13.20.1. Maximum Net Response

The 1987 follow-up examination analysis found that Ranch Hands with later tours of duty had increased maximum PHA net response values as 1987 dioxin levels increased.

13.20.2. Net Response

Among heavy drinkers who participated in the 1987 follow-up examination, Ranch Hands had a lower average PHA net response value than Comparisons. Ranch Hands in the background dioxin category who were heavy drinkers had a greater average PHA net response than their Comparison counterparts.

PHA net response values among Ranch Hands who were the heaviest lifetime drinkers with later tours of duty increased with increasing 1987 dioxin levels. PHA net response values increased with increasing initial dioxin among the heaviest lifetime drinkers and decreased with increasing initial dioxin among nondrinkers.

13.21. SKIN TEST DIAGNOSIS, COMPOSITE

Analysis of 1987 follow-up examination data showed that among all participants and among the heaviest lifetime cigarette smokers, Ranch Hands had a greater prevalence of composite skin test abnormalities than Comparisons.

Analyses of data from the 1992 follow-up examination found that a greater percentage of Ranch Hands in the background dioxin category than Comparisons had an abnormal composite skin test diagnosis.

13.22. ARTICLE

13.22.1. Serum Dioxin and Immunologic Response in Veterans of Operation Ranch Hand

In this article, immune response in relation to dioxin level was studied on the attendees at the AFHS 1992 follow-up examination (8). Delayed-skin hypersensitivity skin test responses to *Candida albicans*, mumps, *Trichophyton*, and a bacterial antigen made from lysed *Staphylococcus aureus* were analyzed. Lymphocyte measurements included total lymphocyte counts; T-cell (CD3, CD4, CD5, and CD8), B-cell CD20), and NK-cell (CD16 and CD56) subsets; and expression of the activation antigen CD25 on CD3 T-cells. In addition, serum concentrations of IgA, IgG, and IgM, monoclonal immunoglobulins and a broad range of autoantibodies (rheumatoid factor, antinuclear antibody, smooth muscle autoantibody, mitochondrial autoantibody, parietal cell autoantibody and thyroid microsomal autoantibody) were analyzed. None of these indicators reflected a consistent or meaningful relation between serum dioxin and altered immune function.

13.23. CONCLUSION

The indexes of immune response analyzed represented a broad spectrum of standard clinical tests of the immune function. Although many statistically significant findings were listed, many were just in isolated subpopulations, values were increased in one exam and then decreased in another, and findings rarely occurred in the same group in different examinations. An article on immune response and dioxin levels in 1992 examination attendees also did not show consistent or meaningful relation between serum dioxin and altered immune function. Therefore, there was no evidence of a consistent relation between dioxin exposure and immune system alteration in Ranch Hand veterans

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14. NEOPLASIA ASSESSMENT

14.1. INTRODUCTION

Many types of cancer are thought to be induced by chlorophenols, phenoxy herbicides, and dioxin. Although herbicides have been determined to be carcinogenic in animal studies, the exposure required for malignant transformation of normal cells and the types of tumors produced are species-dependent. Therefore, while animal studies provide conclusive evidence on the carcinogenic potential of dioxin, the determination of causality in humans remains to be established.

Many studies have assessed the carcinogenic potential of dioxin in humans. While the cumulative exposure data from human studies have not been entirely consistent, associations between dioxin exposure in humans and an increased risk of developing cancers of the skin, lung, bladder, kidney, connective tissue, and lymphatic system have been reported.

During the health interview at all six AFHS examinations, study participants were asked a series of questions on the occurrence of cancer. A medical records review was conducted to confirm reported neoplasms and identify any unreported neoplasms. The data were combined to form a complete lifetime neoplasia history for each participant. These data were the basis of the majority of the analysis for the neoplasia assessment (1-7). The neoplasia assessment itself was based on the occurrence of neoplasms (both benign and malignant) after service in SEA.

Some possible neoplasms were discovered by the physicians at the physical examination. Contingent upon participant authorization, suspicious skin lesions were biopsied and the pathology determined; no other invasive procedures were used to detect neoplasms.

For chest x-ray findings needing follow-up at a separate physical examination, the AFHS staff made every effort to contact and encourage participants to see their primary physicians. The participants were then recontacted to determine whether a final diagnosis was available, and, if so, results were included in the analysis.

In the AFHS examination reports, skin neoplasms were analyzed by category (behavior); according to the following four categories:

- All skin neoplasms at the 1985 - 2002 follow-up examinations
- Malignant skin neoplasms at all six physical examinations
- Benign skin neoplasms at the 1985 - 2002 follow-up examinations
- Skin neoplasms of uncertain behavior or unspecified nature at the 1985 - 2002 follow-up examinations.

The analyses of malignant skin neoplasms were conducted for all sites combined and by the following cell types:

- Basal cell carcinoma at all six physical examinations
- Squamous cell carcinoma at all six physical examinations
- Sun exposure-related neoplasm (basal cell carcinoma, squamous cell carcinoma, melanoma, and malignant epithelial neoplasms not otherwise specified) at 1985 and 1987 follow-up physical examinations

- Nonmelanoma (basal cell carcinoma, squamous cell carcinoma, and malignant epithelial neoplasms not otherwise specified) at the 1992 - 2002 follow-up physical examinations
- Melanoma at all six physical examinations.

Systemic neoplasms were analyzed by category; in particular, the analyses were conducted according to the following four categories:

- All systemic neoplasms
- Malignant systemic neoplasms
- Benign systemic neoplasms
- Systemic neoplasms of uncertain behavior or unspecified nature.

The analyses of malignant systemic neoplasms also were conducted based on the site of the neoplasms. The various sites examined are described later in this chapter.

In addition, analyses were performed on all skin and systemic neoplasms, regardless of category or site, and all malignant neoplasms, which was a combination of malignant skin and malignant systemic neoplasms.

The prostate-specific antigen (PSA) test, a marker for adenocarcinoma of the prostate, is increased with prostate cancer but may be increased in benign entities. Each participant had a PSA test at the 1992 - 2002 follow-up examinations.

The following journal articles were written by AFHS staff and their colleagues:

- Serum dioxin and cancer in veterans of Operation Ranch Hand (8)
- Cancer in US Air Force veterans of the Vietnam War (9)
- Did TCDD exposure or service in Southeast Asia increase the risk of cancer in Air Force Vietnam veterans who did not spray Agent Orange? (10)
- Prostate cancer in USAF veterans of the Vietnam War (11).

The IOM Committee, in their biennial report [1994-2004], *Veterans and Agent Orange*, concluded that there was "sufficient" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. The evidence for an association with respiratory cancers, prostate cancer, and multiple myeloma was considered "limited/suggestive" (12-17). In the 2002 *Veterans and Agent Orange* update, the epidemiologic evidence was considered sufficient concerning chronic lymphocytic leukemia based primarily on studies of agricultural workers (16). This finding remained unchanged in the 2004 update (17).

The following chart lists the variables that were analyzed for the neoplasia assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
PSA					**X**	X	X
Skin Neoplasms							
All		X	X	X	**X**	**X**	**X**
Malignant	**X**	X	X	X	**X**	X	**X**

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Basal Cell Carcinoma	X	**X**	**X**	**X**	**X**	**X**	**X**
Fibrosarcoma	X						
Melanoma	X	X	X	X	X	X	X
Nonmelanoma					X	**X**	**X**
Squamous Cell Carcinoma	X	X	X	X	X	X	X
Sun Exposure-Related		X	**X**	**X**			
Benign		X	X	X	X	**X**	X
Uncertain Behavior or Unspecified Nature		X	X	X	X	X	**X**
Systemic Neoplasms							
All		X	X	**X**	X	X	X
All Stomach							X
Malignant		**X**	X	**X**	**X**	**X**	**X**
Bone and Articular Cartilage	X						X
Brain			X	X	X	X	X
Bronchus and Lung	X	X	X	X	X	**X**	**X**
Carcinoma In Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and Other Male Genitals, Bladder, and Other and Nonspecified Urinary)			X	X	X	X	**X**
Colon and Rectum		X	X	X	**X**	X	**X**
Connective and Other Soft Tissues		X			X	X	X
Digestive Organ, Peritoneum, and Esophagus	X	X			X	X	X
Eye, Ear, Face, Head, and Neck		X	X	X	**X**	X	X
Hodgkin's Disease	X	X	X	X	X	X	X
Ill-Defined Sites		X	X	X	X	X	X
Kidney and Ureter							X
Leukemia		X	X	X	X		X
Lip, Oral Cavity, Pharynx, and Larynx	X	X	X	X	X	X	X
Liver						**X**	X
Lymphoreticular Sarcoma							X
Multiple Myeloma					X		X
Non-Hodgkin's Lymphoma		X			X	X	X
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	X		X	X	X	X	X
Penis and Other Male Genital Organs	X						**X**
Prostate		X	X	X	**X**	X	**X**
Soft Tissue Sarcoma		X					
Stomach							X
Testicles		X	X	X	X	X	X
Thymus, Heart, and Mediastinum			X	X	X	X	X
Thyroid Gland		X	X	X	X	X	X
Urinary System		X	X	**X**	X	**X**	**X**
Benign		X	X	X	X	**X**	X
Uncertain Behavior or Unspecified Nature		X	X	X	**X**	X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Skin and Systemic Neoplasms							
All		X	X	X	**X**	X	**X**
Malignant						**X**	**X**

14.2. PROSTATE-SPECIFIC ANTIGEN (PSA)

The analysis of the 1992 follow-up examination data showed that the prevalence of abnormally high PSA levels increased with increasing 1987 dioxin among Ranch Hand participants who did not report exposure to degreasing chemicals.

14.3. SKIN NEOPLASMS

14.3.1. All Skin Neoplasms

When the 1992 follow-up examination data were analyzed, the prevalence of any type of skin neoplasm was higher for Ranch Hands in the low dioxin category than Comparisons.

In the analysis of the 1997 follow-up examination data, the prevalence of any type of skin neoplasm was higher in Ranch Hands than Comparisons among all participants, among officers, and among enlisted flyers. Ranch Hands in the background and low dioxin categories had a higher prevalence of any type of skin neoplasm than Comparisons.

The analysis of the 2002 follow-up examination data showed that among all participants, Ranch Hands had a higher prevalence of any type of skin neoplasm than Comparisons. Ranch Hands in the low dioxin category also had a higher prevalence of any type of skin neoplasm than Comparisons.

14.3.2. Malignant Skin Neoplasms

The analysis of the 1982 baseline examination data showed that Ranch Hands had a higher prevalence of a malignant skin neoplasm than Comparisons.

The 1992 follow-up examination data analysis showed that, among participants who did not report exposure to industrial chemicals, Ranch Hands in the low dioxin category had a higher prevalence of a malignant skin neoplasm than Comparisons.

A higher percentage of Ranch Hands in the low dioxin category than Comparisons had a malignant skin neoplasm in the 2002 follow-up examination data analysis.

14.3.2.1. Basal Cell Carcinoma

In 1985, the analysis of the follow-up examination data showed a higher prevalence of basal cell carcinoma among Ranch Hand enlisted flyers than Comparison enlisted flyers.

The analysis of the 1987 follow-up examination data showed a higher percentage of Ranch Hands with basal cell carcinoma than Comparisons. Also, Ranch Hands in the background and low dioxin categories had a higher prevalence of basal cell carcinoma at multiple sites than Comparisons. The prevalence of basal cell carcinoma on sites that were not specified increased with increasing initial dioxin among Ranch Hand enlisted flyers. In addition, Ranch Hands in the low dioxin category had a higher prevalence than Comparisons of basal cell carcinoma on sites that were not specified. Among enlisted flyers,

however, Ranch Hands in the high dioxin category had a higher prevalence of basal cell carcinoma on sites that were not specified than Comparisons.

The analysis of the 1992 follow-up examination data showed that the prevalence of basal cell carcinoma on the trunk increased with increasing 1987 dioxin levels among Ranch Hand participants who did not report exposure to insecticides.

The 1997 follow-up examination data analysis showed a higher prevalence of basal cell carcinoma in Ranch Hand enlisted flyers than Comparison enlisted flyers. In addition, Ranch Hands in the low dioxin category had a higher prevalence of basal cell carcinoma than Comparisons. The prevalence of basal cell carcinoma on the trunk for Ranch Hands also increased with increasing 1987 dioxin levels.

At the 2002 follow-up examination, among all participants and officers, Ranch Hands had a higher prevalence of basal cell carcinoma than Comparisons. Ranch Hands in the low dioxin category also had a higher prevalence of basal cell carcinoma than Comparisons.

14.3.2.2. Nonmelanoma

The 1997 follow-up examination showed that Ranch Hand enlisted flyers had a higher prevalence of a nonmelanoma malignant skin neoplasm than Comparison enlisted flyers.

Ranch Hands had a higher prevalence of a nonmelanoma malignant skin neoplasm than Comparisons in the analysis of the 2002 follow-up examination data; this difference was seen primarily in officers. In addition, a greater percentage of Ranch Hands in the low dioxin category had a nonmelanoma malignant skin neoplasm than Comparisons.

14.3.2.3. Sun Exposure-Related Malignant Skin Neoplasm

At the 1987 follow-up examination, Ranch Hands had a higher prevalence of a sun exposure-related malignant skin neoplasm than Comparisons. Ranch Hands in the low dioxin category had a higher prevalence of this type of malignant skin neoplasm than Comparisons on sites that were not specified. Among enlisted flyers, Ranch Hands in the high dioxin category also had a greater prevalence of a sun exposure-related malignant skin neoplasm than Comparisons on sites that were not specified. In addition, the prevalence of Ranch Hand enlisted flyers with a sun exposure-related malignant skin neoplasm on sites that were not specified increased with increasing initial dioxin.

14.3.3. Benign Skin Neoplasms

The analysis of the 1997 follow-up examination data showed that the prevalence of a benign skin neoplasm was higher in Ranch Hands than in Comparisons among officers. Ranch Hands in the background dioxin category also had a greater prevalence of a benign skin neoplasm than Comparisons.

14.3.4. Skin Neoplasms of Uncertain Behavior or Unspecified Nature

The 2002 follow-up examination data analysis showed that the prevalence of a skin neoplasm of uncertain behavior or unspecified nature was greater for Ranch Hands in the low dioxin category than for Comparisons.

14.4. SYSTEMIC NEOPLASMS

14.4.1 All Systemic Neoplasms

The 1987 follow-up examination data analysis showed that the prevalence of any type of systemic neoplasm in Ranch Hands increased with increasing initial dioxin. The prevalence of any type of systemic neoplasm in Ranch Hands with later tours also increased with increasing 1987 dioxin.

14.4.2. Malignant Systemic Neoplasms

The 1985 follow-up examination data analysis showed that Ranch Hand enlisted flyers had a higher prevalence of a malignant systemic neoplasm than Comparison enlisted flyers.

Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm than Comparisons in the analysis of the 1987 follow-up examination data.

The analysis of the 1992 follow-up examination data showed that the prevalence of a malignant systemic neoplasm increased with increasing 1987 dioxin levels among Ranch Hands who did not report exposure to degreasing chemicals.

Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm than Comparisons at the 1997 follow-up examination.

The 2002 follow-up examination data analysis showed Ranch Hand officers had a higher prevalence of a malignant systemic neoplasm than Comparison officers. In addition, a higher percentage of Ranch Hands in the low dioxin category had a malignant systemic neoplasm than Comparisons.

14.4.2.1. Bronchus and Lung

At the 1997 and 2002 follow-up examinations, Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the bronchus and lung than Comparisons.

14.4.2.2. Carcinoma in Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and Other Male Genitals, Bladder, and, Other and Nonspecified Urinary)

The analysis of the 2002 follow-up examination data showed that a higher percentage of Ranch Hands in the low dioxin category had a carcinoma in situ than Comparisons.

14.4.2.3. Colon and Rectum

The 1992 and 2002 follow-up examination data analyses showed that the prevalence of a malignant systemic neoplasm of the colon and rectum was higher among Ranch Hands in the low dioxin category than among Comparisons. The analysis of the 2002 follow-up examination data also showed that the prevalence of a malignant systemic neoplasm of the colon and rectum was higher for Ranch Hand officers than Comparison officers.

14.4.2.4. Eye, Ear, Face, Head, and Neck

The 1992 follow-up examination data analysis showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the eye, ear, face, head, or neck than Comparisons among moderate lifetime cigarette smokers (more than 0 pack-years but no more than 10 pack-years) and among participants who did not report exposure to degreasing chemicals.

14.4.2.5. Liver

At the 1997 follow-up examination, the prevalence of a malignant systemic neoplasm of the liver among Ranch Hands increased with increasing 1987 dioxin levels.

14.4.2.6. Malignant Systemic Neoplasms of the Penis and Other Male Genital Organs

The 2002 follow-up examination data analysis showed that the prevalence of a malignant systemic neoplasm of the penis and other male genital organs increased with increasing 1987 dioxin levels.

14.4.2.7. Prostate

When the 1992 follow-up examination data were analyzed, the findings showed that the prevalence of a malignant systemic neoplasm of the prostate increased with increasing 1987 dioxin levels among Ranch Hand participants who did not report exposure to degreasing chemicals.

At the 2002 follow-up examination, Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the prostate than Comparisons.

*14.4.2.8. Urinary Syste*m

The analyses of 1987 and 1997 follow-up examination data showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the urinary system than Comparisons.

At the 2002 follow-up examination, Ranch Hands had a higher prevalence of a malignant systemic neoplasm of the urinary system than Comparisons, primarily among officers. The prevalence of a malignant systemic neoplasm of the urinary system among Ranch Hands increased with increasing initial dioxin. In addition, Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the urinary system than Comparisons.

14.4.3. Benign Systemic Neoplasms

The prevalence of a benign systemic neoplasm in Ranch Hands increased with increasing initial and 1987 dioxin levels at the 1997 follow-up examination.

14.4.4. Systemic Neoplasms of Uncertain Behavior or Unspecified Nature

The analysis of the 1992 follow-up examination data showed that the prevalence of a systemic neoplasm of uncertain behavior or unspecified nature increased with increasing 1987 dioxin among Ranch Hands who reported exposure to asbestos.

14.5. SKIN AND SYSTEMIC NEOPLASMS

14.5.1. All Skin and Systemic Neoplasms

At the 1992 follow-up examination, the prevalence of any type of skin or systemic neoplasm increased with increasing 1987 dioxin levels among Ranch Hand participants with hazel or green eyes.

In the analysis of the 2002 follow-up examination data, a higher percentage of Ranch Hands in the low dioxin category had an occurrence of any type of skin or systemic neoplasm than Comparisons.

14.5.2. Malignant Skin and Systemic Neoplasms

Both the 1997 and the 2002 follow-up examination data analyses showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant skin or systemic neoplasm than Comparisons.

14.6. ARTICLES

14.6.1. Serum Dioxin and Cancer in Veterans of Operation Ranch Hand

A 1999 *American Journal of Epidemiology* article (8) described results of an analysis of cancers for all AFHS veterans who attended at least one of the 1982, 1985, 1987, or 1992 examinations and who had a dioxin measurement. All cancers, among these veterans, verified as of July 1997 were included. Analysis of cancer prevalence and latency was conducted for all cancers, skin cancers, and cancer at all sites other than the skin. Subgroups of skin cancers and cancer at all sites other than the skin were also analyzed. An inherent limitation of the AFHS was that low statistical power existed to detect an effect for specific or rare cancers.

No evidence of a dose-response pattern or of a latency effect existed for all cancers or skin cancers. The risk of cancer at sites other than the skin was not increased for Ranch Hands in the high dioxin category, but an increased risk for Ranch Hands in the low dioxin category who had ended their service in SEA within the past 20 years was observed. Kidney or bladder cancer was increased for Ranch Hands in the low dioxin category. Ranch Hands in the low dioxin category, but not in the high dioxin category, had an earlier time to onset of cancer of any type. These results were inconsistent with a National Institute for Occupational Safety and Health study of workers at 12 plants in the United States that produced chemicals contaminated with dioxin (18) and suggest that the increased risk may not have been caused by dioxin exposure. Overall, no consistent evidence of a dose-response relation and no significant increase in cancer risk existed in the high dioxin category, the subgroup of greatest interest based on average dioxin levels.

14.6.2. Cancer in US Air Force Veterans of the Vietnam War

An analysis of cancers for all AFHS veterans who attended at least one of the 1982, 1985, 1987, 1992, or 1997 examinations was conducted and the results were reported in a 2004 journal article (9). The effects of time spent in SEA, the calendar period of service, and the percentage of SEA service spent in Vietnam were explored relative to cancer in AFHS participants. The conditions included cancers verified as of 31 December 1999. Cancer morbidity was classified by anatomical site using the Surveillance, Epidemiology, and End Results (SEER) section of the National Cancer Institute (NCI) classification system. The SEER categories included all anatomical sites except basal cell and squamous cell carcinoma. Cancer incidence and mortality were considered separately. External contrasts against U.S. national cancer rates and internal analyses by dioxin category were conducted. To maximize available data, all AFHS veterans who attended at least one of the 1982, 1985, 1987, 1992, or 1997 examinations were used for external analysis, whereas the internal measurements used the subset of the participants from the external analyses who additionally had a dioxin measurement.

External contrasts found that the incidences of melanoma and prostate cancer were increased among white Ranch Hand veterans; the same pattern was found when the analysis was restricted to white Ranch Hand participants whose tour of duty occurred between 1966 and 1970, the period of heaviest Agent Orange spraying. The incidence of prostate cancer also was increased among white Comparison veterans; the same pattern was found when the analysis was restricted to Comparison participants whose tour of duty occurred between 1966 and 1970. No significant increases in cancer mortality were found relative to national rates.

Two internal analyses were conducted to address concerns that Comparisons who spent time in Vietnam may have developed cancer. The first analysis was restricted to participants who spent at most 2 years in SEA and the second analysis to Ranch Hands who spent 100 percent of their SEA tours in Vietnam and to Comparisons who spent 0 percent of their SEA tours in Vietnam. Categorization by time spent in SEA approximated categorization by the percentage of SEA service spent in Vietnam. Stratification by the percentage of SEA service spent in Vietnam provided a clearer dichotomy on the Vietnam experience at the expense of a reduction in sample size. Among veterans who spent at most 2 years in SEA, the risk of cancer at any site, prostate cancer, and melanoma was increased in the high dioxin category. Among Ranch Hands who spent 100 percent of their SEA tours of duty in Vietnam, the risk of cancer at any site was increased in the low and high dioxin categories relative to Comparisons who spent 0 percent of their SEA tours of duty in Vietnam.

14.6.3. Did TCDD Exposure or Service in Southeast Asia Increase the Risk of Cancer in Air Force Vietnam Veterans Who Did Not Spray Agent Orange?

The effects of time spent in SEA and dioxin level were explored relative to cancer in AFHS Comparison participants and reported in a 2005 journal article by Pavuk et al. (10). Cancer morbidity was classified by anatomical site using the SEER classifications. The SEER categories included all anatomical sites except basal cell and squamous cell carcinoma. The analysis was based on Comparisons who had a dioxin measurement and attended at least one of the six AFHS examinations in 1982, 1985, 1987, 1992, 1997, and 2002. An increased risk of all-sites cancer and trends of increased risks of all SEER sites cancer and melanoma with dioxin were found in AFHS Comparison participants. These veterans had background dioxin levels and were not occupationally exposed to Agent Orange or other herbicides. The results suggested that dioxin acts as an initiator or a promoter of carcinogenesis at low levels or may be a surrogate for other unmeasured risk factors associated with an increased risk of cancer. The results indicated an interrelationship between all-sites cancer, dioxin, and service in SEA, and further suggested that a combination of factors related to time spent in SEA were probably involved. Service in SEA was itself a risk factor for prostate cancer in these AFHS Comparison participants, independent of dioxin exposure.

14.6.4. Prostate cancer in USAF veterans of the Vietnam War

The effects of exposure to dioxin and prostate cancer were explored in AFHS participants and reported in a 2005 journal article by Pavuk et al. (11). The analysis was based on participants who attended at least one of the examinations in 1982, 1985, 1987, 1992, 1997 or 2002 and who had a dioxin level. The time to prostate cancer diagnoses was calculated as the time from 1 January 1982 to the earliest date of the first prostate cancer diagnosis, death, or 31 December 2003. An analysis by time served in Southeast Asia was also conducted. There was no overall increase in the risk of prostate cancer in Ranch Hand veterans versus the Comparisons. There was a positive association in Ranch Hands in the high dioxin category who served in SEA before 1969 when more contaminated herbicides were used, but the number of cases was small. No increase risk of prostate cancer was observed within Ranch Hand group in association with dioxin or time served in SEA. However, in Comparisons time served in SEA was associated with an increased risk of prostate cancer. Thus, suggesting that longer service in SEA and exposures other than dioxin may have increased the risk of prostate cancer in the Comparisons.

14.7. CONCLUSION

Statistical power becomes an issue in a study with a population the size of the AFHS. A study with a population of the approximately 2,000 veterans who completed physical examinations lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma) because such events are

unlikely to occur in large numbers in a group this small. While certain occupational toxicants have a clear diagnostic pathology that is virtually nonexistent in the absence of the causative agent, other toxicants merely increase the risk of nondiagnostic pathology. For example, the AFHS likely would not discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology.

From the analysis of the physical examination data published in the examination reports the associations between herbicide exposure or dioxin levels and the likelihood of developing cancer were seen primarily for Ranch Hand officers and Ranch Hands in the low dioxin category. No associations were observed for Ranch Hand enlisted groundcrew, the military occupational category that had the highest median level of exposure to dioxin. Other risk and operational factors discussed in published articles did not show consistent associations in Ranch Hands but did show some associations in the Comparisons. Results were adjusted for relevant risk and demographic factors where possible.

Based on a journal article published in 2004 (9), the incidences of melanoma and prostate cancer were increased among white Ranch Hand veterans. The same pattern was found when the analysis was restricted to white Ranch Hand participants whose tour of duty occurred between 1966 and 1970, the period of heaviest Agent Orange spraying. The incidence of prostate cancer was also increased among white Comparison veterans; the same pattern was found when the analysis was restricted to Comparison participants whose tour of duty occurred between 1966 and 1970. No increase in cancer mortality relative to national rates was found.

Among veterans who spent at most 2 years in SEA, the risk of cancer at any site, prostate cancer, and melanoma was increased in the high dioxin category. Among Ranch Hands who spent 100 percent of their SEA tours of duty in Vietnam, the risk of cancer at any site was increased in the low and high dioxin categories relative to Comparisons who spent 0 percent of their SEA tours of duty in Vietnam.

Based on a journal article published in 2005 (10), an increased risk of all-sites cancer and trends of increased risks of all SEER sites cancer and melanoma with dioxin were found in AFHS Comparison participants. These veterans had background dioxin levels and were not occupationally exposed to Agent Orange or other herbicides. The results suggested that dioxin acts as an initiator or a promoter of carcinogenesis at low levels or may be a surrogate for other unmeasured risk factors associated with an increased risk of cancer. The results indicated an interrelationship between all-sites cancer, dioxin, and service in SEA, and further suggested that a combination of factors related to time spent in SEA were probably involved. Service in SEA was itself a risk factor for prostate cancer in these AFHS Comparison participants, independent of dioxin exposure.

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15. NEUROLOGY ASSESSMENT

15.1. INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and dioxin. Animal research and studies of humans exposed to high levels of dioxin imply that the peripheral nervous system is a target organ for acute dioxin toxicity. The recognized acute neurotoxicity of these chemicals and the prevalence of neurological complaints among veterans were primary factors in the decision to place a major emphasis on the neurological evaluation of participants in the AFHS.

Analyses were performed to assess the neurological function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). The neurology assessment was based on extensive physical examination data on cranial nerve function, peripheral nerve status, and central nervous system (CNS) coordination processes. Analyses were adjusted for age, race, military occupation, and known risk factors, such as diabetes. The questionnaire captured data on the occurrence of neurological disorders. Medical records reviews were conducted to confirm reported neurological conditions and to identify any unreported conditions for each participant. Neurological diseases and disorders were classified into three categories across all six examinations: hereditary and degenerative diseases, inflammatory diseases, and peripheral disorders. The category, other neurological disorders was analyzed at the 1985 through 2002 physical examinations. Other neurological disorders consisted mainly of unspecified encephalopathies, but conditions such as multiple sclerosis and other demyelinating diseases of the CNS, hemiplegia, other paralytic syndromes, epilepsy, migraine, catalepsy or narcolepsy, other conditions of the brain, and other unspecified disorders of the CNS were included.

Conduction velocity of the distal ulnar (below the elbow), peroneal, and proximal ulnar (above the elbow) were analyzed in 1982. Disorders of the ear and eye were analyzed at the 1982 through 1987 examinations. Hearing loss, external otitis and tympanic membrane disorders were analyzed only at the 1987 examination. At the 2002 examination, possible and probable peripheral neuropathy were analyzed based on three outcomes: both left and right Achilles reflexes were absent, reaction to a pinprick was abnormal on both the left and right feet, and both left and right ankle vibrations were abnormal. Possible peripheral neuropathy was defined to be present if one of the above three conditions held. Probable peripheral neuropathy was defined as present if at least two of the three conditions held.

15.1.1. Central Nervous System (CNS) Coordination Processes

At all six examinations, the evaluation of CNS coordination processes was based on the analyses of coordination, gait, and tremor. Coordination was a composite index defined as normal if the Romberg sign, finger-nose-finger and heel-knee-shin coordination processes, and rapidly alternating movements of pronation and supination of hands were normal. The Romberg sign variable was equivalent to the "balance" variable analyzed as part of the cranial nerve function assessment (see 15.1.2). Tremor was examined for the left and right upper and lower extremities. Abnormal tremors included resting, essential, intention, and other tremors. For tremors and coordination, a result was classified as normal if all determinations were normal and abnormal if at least one determination was abnormal. The gait variable was based on the examining physician's assessment of the participant's gait. An abnormal gait included conditions such as broad-based, small-stepped, ataxic, or other irregular gait patterns. A CNS index for the 1985, 1987, 1992, 1997 and 2002 follow-up examinations was constructed and based on a

composite variable of tremor, coordination, and gait. This index was coded as normal if all three of the components were normal and abnormal if otherwise.

15.1.2. Cranial Nerve Function

At all six examinations, the evaluation of cranial nerve function was based on the following 14 variables: balance, corneal reflex, facial sensation, gag reflex, jaw clench, light reaction, ocular movement, palate and uvula movement, palpebral fissure, smell, smile, speech, tongue position relative to midline, and visual fields. Shoulder shrug was added to the evaluation of cranial nerve function at the 2002 follow-up examination. All of these variables were scored as normal or abnormal, except for jaw clench and palate and uvula movement, which were scored as symmetric or deviated. For variables with left and right determinations, the two results were combined to produce a single normal or abnormal result, where normal indicated that both responses were normal, and abnormal indicated that at least one of the responses was abnormal. Abnormal speech conditions included aphasia, dysarthria, agnosia, and other speech abnormalities.

A cranial nerve index for 1985, 1987, 1992, 1997 and 2002 follow-up examinations was created by combining responses for cranial nerve determinations and depending on the year the index included an evaluation of neck movement (1985, 1987, 1992, and 1997) or shoulder shrug (2002). The neck range of motion variable was coded as abnormal if there was a decreased range of motion forward or backward or to the left or right. The cranial nerve index was classified as abnormal if at least one of the determinations was abnormal, and normal if all of the cranial nerve parameters were normal.

15.1.3. Peripheral Nerve Status

At all six examinations, peripheral nerve status was assessed by visual inspection of muscle mass (and palpation, if indicated), light pinprick, three deep tendon reflexes (Achilles, patellar, and biceps), the Babinski reflex, and light touch (cotton sticks). Vibratory sensation as measured at the ankle with a tuning fork of 128 Hz was analyzed at the 1982, 1985 and 1987 examinations. Pinprick, light touch, and ankle vibratory sensation were considered normal if the reaction was normal on both legs. A muscle status variable was constructed using data on bulk; tone of upper and lower extremities; and the strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors. Bulk was classified as either normal or abnormal. Tone was classified as abnormal if there was either a decreased or an increased response on either the left side, right side, or both sides. The strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors was considered abnormal if either the left or right side or both sides were decreased. Composite muscle status was classified as normal if all of the components were normal on both the left and right sides and abnormal if at least one of the components was abnormal on either or both sides.

The Achilles, patellar, and biceps reflexes were divided into three categories: "absent," "sluggish," and "active or very active." The categories of "active" and "very active" were combined because of the sparse number of participants with very active reflexes. Two contrasts that preserved the ordinal structure of the data were examined: "sluggish or absent" versus "active or very active" (i.e., less than active versus active), and "absent" versus "sluggish, active, or very active" (i.e., reflexes absent versus not absent). When the assessments of the reflex were different between the left and right body side, the more severe condition was assigned. For example, if the left Achilles reflex was sluggish and the right Achilles reflex was absent, the composite Achilles reflex variable was designated as absent.

Pinprick was considered normal if the reaction was normal on both feet and abnormal if the reaction was abnormal on either foot.

15.1.4. Polyneuropathy

For the 1997 follow-up examination, three indices to assess polyneuropathy were based on a severity index. These indices assessed bilateral abnormalities and were considered abnormal only if both the left and right determinations were abnormal. These indices were based on the following seven conditions or sets of conditions:

- Both left and right ankle and toe flexors were abnormal (no=0, yes=1)
- The Romberg sign (equilibratory) was abnormal (no=0, yes=1)
- Both left and right Achilles reflexes were absent (no=0, yes=1)
- Reaction to a light touch was abnormal on both the left and right feet (no=0, yes=1)
- Reaction to a pinprick was abnormal on both the left and right feet (no=0, yes=1)
- Both left and right ankle vibrations were abnormal (no=0, yes=1)
- The position of both the left and right great toe was abnormal (no=0, yes=1).

A polyneuropathy severity index, which ranged from 0 to 7, was constructed as the sum of the above seven scores. The polyneuropathy severity index was classified as mild (index = 0, 1, or 2), moderate (index = 3 or 4), or severe (index = 5, 6, or 7). A second index, termed a polyneuropathy prevalence indicator, was coded as abnormal if the polyneuropathy severity index was at least 1 and normal if the polyneuropathy severity index was 0. This index was also analyzed at the 2002 follow-up examination. A third index, termed a multiple polyneuropathy index, was coded as "abnormal" if the polyneuropathy severity index was at least 2 and "normal" if the polyneuropathy severity index was 0 or 1.

A vibrotactile measurement was performed as part of a collaborative effort with the National Institute of Dental and Craniofacial Research at the 1992 and 1997 follow-up examinations. A Vibratron II® device was used to measure vibrotactile threshold on both the left and right great toes. The Vibratron II® provided a noninvasive means of measuring the sensitivity to vibration of a participant's feet. The left and right great toes were analyzed separately. For each great toe, the average (in log microns) of four of seven trials was determined. The four trials were those remaining after eliminating the results of the first of the seven trials and the high and low readings of the other six results following a method-of-limits protocol (15).

In addition, at the 1997 follow-up examination, a confirmed polyneuropathy index was constructed as follows:

If at least two of the following three conditions held,

- Both left and right Achilles reflexes were absent
- Reaction to a pinprick was abnormal on both the left and right feet
- Both left and right ankle vibrations were abnormal

and the minimum of the left and right toe vibrotacle averages (in log microns) was greater than 4.02, the confirmed polyneuropathy index was coded as abnormal. If the minimum vibrotactile measurement was less than or equal to 4.02, or no more than one of the above conditions was present, the confirmed polyneuropathy index was coded as normal. The value of 4.02 was determined by taking the minimum value of the left and right great toe average for each participant and using the 90^{th} percentile of the minimum values for Comparisons.

15.1.5. Article

The following journal article on polyneuropathy in AFHS veterans was written by AFHS staff and their colleagues:

- Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand (8).

15.1.6. Institute of Medicine Veterans and Agent Orange Reports

In the 1996 IOM *Veterans and Agent Orange* update (9), the Committee concluded that there is "limited/suggestive" evidence of an association between exposure to certain herbicides used in Vietnam and the development of an acute or subacute transient peripheral neuropathy. This conclusion remained unaltered in the 2002 and 2004 IOM *Veterans and Agent Orange* updates (10, 11). The evidence regarding the association between exposure to dioxin and disorders involving persistent peripheral neuropathy, or motor or coordination deficits was considered inadequate or insufficient (10, 11).

In the 1994 *Veterans and Agent Orange* report (12), the IOM Committee concluded that there was inadequate or insufficient evidence to determine whether an association existed between dioxin and motor coordination problems. This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (11).

A persisting concern existed regarding the role of herbicides and pesticides in the pathogenesis of Parkinson's disease. The relation between pesticide exposure and Parkinson's disease was evaluated in the 1996, 1998, 2000, 2002, and 2004 *Veterans and Agent Orange* updates (9-11, 13-14). Some indication of an association between Parkinson's disease and herbicides and pesticides was seen based on a review of 30 epidemiologic studies, most of which were case-control studies focusing on occupational exposure. An association of Parkinson's disease with exposure to dioxin, however, was not reported in any of these studies. Therefore, the 2002 IOM Committee considered the evidence for an association of Parkinson's disease with exposure to dioxin to be inadequate or insufficient (10); this conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (11).

The following chart lists the variables that were analyzed for the neurology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Conduction Velocity: Distal Ulnar	X						
Conduction Velocity: Peroneal	X						
Conduction Velocity: Proximal Ulnar	X						
Ear Disorders	X	X	X				
Eye Disorders	X	X	X	X			
Hearing Loss				X			
Neurological Disease, Hereditary and Degenerative	X	X	X	X	X	X	**X**
Neurological Disease, Inflammatory	X	X	X	X	X	**X**	X
Neurological Disorders, Other		X	X	**X**	X	X	X
External Otitis				X			
Peripheral Disorders	X	X	X	X	**X**	**X**	X
Tympanic Membrane Disorder				X			
Central Nervous System (CNS) Coordination Processes							
CNS Index		**X**	X	**X**	X	X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Coordination	X	X	**X**	**X**	X	X	**X**
Gait	X	X	X	X	**X**	X	X
Tremor	X	X	X	**X**	X	X	X
Cranial Nerve Function							
Balance/Romberg Sign	X	X	X	X	X	X	**X**
Corneal Reflex	X	X	X	X	X	X	X
Cranial Nerve Index		X	**X**	**X**	**X**	X	**X**
Facial Sensation	X	X	X	X	X	X	**X**
Gag Reflex	X	X	X	X	X	X	X
Jaw Clench	X	X	X	X	X	X	X
Light Reaction	X	X	X	X	X	X	X
Neck Range of Motion	X	X	X	**X**	X	**X**	
Ocular Movement	X	X	X	X	X	X	X
Palate and Uvula Movement	X	X	X	X	X	X	X
Palpebral Fissure	X	X	X	X	X	X	X
Shoulder Shrug							X
Smell	X	X	X	X	**X**	X	X
Smile	X	X	X	X	X	X	X
Speech	X	X	X	X	X	X	X
Tongue Position Relative to Midline	X	X	X	X	X	X	X
Visual Fields	X	X	X	X	X	**X**	**X**
Peripheral Nerve Status							
Muscle Status	X	X	X	X	X	**X**	X
Pinprick	X	X	X	**X**	**X**	X	**X**
Reflexes: Achilles	X	X	X	X	**X**	X	**X**
Reflexes: Babinski	X	X	X	X	X	X	X
Reflexes: Biceps	X	X	X	X	X	X	X
Reflexes: Patellar	X	X	X	X	**X**	**X**	**X**
Touch, Light	X	X	X	X	X	X	X
Vibration at the ankle, 128hz	X	X	X	X			
Polyneuropathy							
Peripheral Neuropathy, Possible							X
Peripheral Neuropathy, Probable							X
Polyneuropathy Index, Confirmed						**X**	
Polyneuropathy Index, Multiple						**X**	
Polyneuropathy Prevalence Indicator						**X**	X
Polyneuropathy Severity Index						**X**	
Vibrotactile Threshold Measurement of Great Toes					**X**	X	

15.2. NEUROLOGICAL DISEASE, HEREDITARY AND DEGENERATIVE

Based on data collected at the 2002 follow-up examination, more Ranch Hand officers than Comparison officers had hereditary and degenerative neurological disorders after service in SEA.

15.3. NEUROLOGICAL DISEASE, INFLAMMATORY

Based on data collected at the 1997 follow-up examination, more Ranch Hands than Comparisons had inflammatory diseases after service in SEA. The prevalence of inflammatory diseases was increased in the background, low, and high dioxin categories. The increase in Ranch Hands was due to seven Ranch Hands and one Comparison who have had an inflammatory disease since service in SEA. Further review of these diseases revealed that three of the seven Ranch Hands had meningitis caused by a bacterial infection. The Comparison had encephalitis of unknown cause. This review suggested that this finding was unrelated to herbicide or dioxin exposure.

15.4. NEUROLOGICAL DISORDERS, OTHER

Based on data collected at the 1987 follow-up examination, as 1987 and initial dioxin increased in Ranch Hands with later tours of duty, the prevalence of other neurological disorders after service in SEA increased.

15.5. PERIPHERAL DISORDERS

At the 1992 follow-up examination, among moderate lifetime drinkers (>0-40 drink-years), the prevalence of peripheral disorders after service in SEA increased with increasing levels of 1987 dioxin. At the 1997 follow-up examination, in Ranch Hands the prevalence of peripheral disorders increased with increasing 1987 dioxin.

15.6. CENTRAL NERVOUS SYSTEM (CNS) COORDINATION PROCESSES

15.6.1. CNS Index

Ranch Hands had more abnormalities of the CNS index at the 1985 follow-up examination than Comparisons. At the 1987 follow-up examination, the prevalence of an abnormal CNS index in Ranch Hands increased as initial dioxin increased. This finding was also seen in older Ranch Hands. In addition, as 1987 dioxin in Ranch Hands with later tours of duty increased, the prevalence of a CNS index abnormality increased.

15.6.2. Coordination

Ranch Hands had a higher prevalence of a coordination abnormality at the 1987 follow-up examination than Comparisons. Further analysis on subsets of these participants showed that the increase was in Ranch Hand enlisted groundcrew who reported exposure to insecticides. Ranch Hands in the high dioxin category had a higher prevalence of a coordination abnormality than Comparisons. In particular, the increase was most pronounced in older Ranch Hands. Also as 1987 dioxin in Ranch Hands with later tours of duty increased, the prevalence of a coordination abnormality increased. The prevalence of an abnormal coordination at the 2002 follow-up examination increased as initial dioxin increased.

15.6.3. Gait

The prevalence of an abnormal gait at the 1992 follow-up examination among older Ranch Hands increased as initial dioxin increased.

15.6.4. Tremor

As 1987 dioxin in older Ranch Hands with later tours of duty increased, the prevalence of an abnormal tremor at the 1987 follow-up examination increased.

15.7. CRANIAL NERVE FUNCTION

15.7.1. Balance/Romberg Sign

The prevalence of an abnormal balance determination in Ranch Hands at the 2002 follow-up examination increased as initial dioxin increased.

15.7.2. Cranial Nerve Index

The prevalence of a cranial nerve index abnormality at the 1987 follow-up examination increased for Ranch Hand diabetics (2-hour postprandial glucose≥200 mg/dL or previously diagnosed as diabetic by a physician) as initial dioxin increased. Ranch Hands with earlier tours of duty showed an increase in cranial nerve index abnormalities as 1987 dioxin levels increased. Neck range of motion abnormalities were included in the definition of the cranial nerve index for analysis at this examination and were the primary source of abnormalities for this index.

Analysis of 1987 follow-up examination data also was done without including neck range of motion in the definition of the cranial nerve index. In this version of the index, Ranch Hands who did not report exposure to insecticides had more abnormalities than Comparisons who did not report exposure to insecticides. When categorizing Ranch Hands according to dioxin levels, these differences were between Ranch Hands and Comparisons and in the low Ranch Hand dioxin category.

Analyses without including neck range of motion in the definition of the cranial nerve index also were performed for the 1992 follow-up examination. The prevalence of an abnormal index in Ranch Hands with normal glucose levels (2-hour postprandial glucose < 140 mg/dL) increased as initial dioxin levels increased. In addition, Ranch Hand enlisted groundcrew had a higher prevalence of abnormalities than Comparison enlisted groundcrew; this increase in Ranch Hands was seen in the background and high dioxin categories.

At the 2002 follow-up examination Ranch Hands showed a higher prevalence of an abnormal index than Comparisons, as did Ranch Hands in the background and low dioxin categories.

15.7.3. Facial Sensation

More Ranch Hands in the low dioxin category had an abnormal facial sensation at the 2002 follow-up examination than Comparisons.

15.7.4. Neck Range of Motion

The prevalence of a neck range of motion abnormality at the 1987 follow-up examination increased for Ranch Hand diabetics (2-hour postprandial glucose≥200 mg/dL or previously diagnosed as diabetic by a physician) as initial dioxin increased. Ranch Hands with earlier tours of duty showed an increase in neck range of motion abnormalities as 1987 dioxin levels increased.

The prevalence of a neck range of motion abnormality was increased for Ranch Hands at the 1997 follow-up examination. This pattern was seen when all participants were analyzed and when analyses were restricted to enlisted flyers. The increase also was observed in the low and high Ranch Hand dioxin categories relative to Comparisons.

15.7.5. Smell

Among participants who did not report exposure to insecticides, more Ranch Hand participants in the low dioxin category had an abnormal sense of smell at the 1992 follow-up examination than Comparisons.

15.7.6. Visual Fields

Among Ranch Hands who participated in the 1997 follow-up examination, the prevalence of abnormal visual fields increased as initial dioxin levels increased. At the 2002 follow-up examination, more Ranch Hands than Comparisons had abnormal visual fields. In particular, the increase appeared in Ranch Hands with background dioxin levels relative to Comparisons.

15.8. PERIPHERAL NERVE STATUS

15.8.1. Muscle Status

More Ranch Hand enlisted groundcrew than Comparison enlisted groundcrew had an abnormal muscle status at the 1997 follow-up examination.

15.8.2. Pinprick

At the 1987 follow-up examination for Ranch Hands with earlier tours of duty, the prevalence of an abnormal reaction to pinprick increased as 1987 dioxin increased. For Ranch Hands who were considered diabetic (2-hour postprandial glucose≥200 mg/dL or previously diagnosed as diabetic by a physician), the prevalence of an abnormal reaction to pinprick at the 1992 follow-up examination increased as 1987 dioxin increased. At the 2002 follow-up examination, Ranch Hands in the high dioxin category had an increased abnormal reaction to pinprick.

15.8.3. Achilles Reflex

A greater prevalence of Ranch Hand nondrinkers in the high dioxin category had an absent Achilles reflex at the 1992 follow-up examination than Comparison nondrinkers. At the 2002 follow-up examination, Ranch Hand officers had an absent or sluggish Achilles reflex more often than Comparison officers.

15.8.4. Patellar Reflex

As 1987 dioxin increased, the prevalence of Ranch Hands with an absent patellar reflex at both the 1992 and 2002 follow-up examinations increased. The prevalence of Ranch Hands with an absent patellar reflex at the 1997 follow-up examination increased as initial dioxin levels increased. The percentage of participants with an absent patellar reflex at the 2002 follow-up examination was increased in Ranch Hands in the high dioxin category.

15.9. POLYNEUROPATHY

15.9.1. Confirmed Polyneuropathy Index

The prevalence of confirmed polyneuropathy index, at the 1997 follow-up examination increased with increasing initial dioxin in Ranch Hands. Ranch Hands in the high dioxin category also had an increased prevalence of confirmed polyneuropathy index.

15.9.2. Multiple Polyneuropathy Index

The prevalence of an abnormal multiple polyneuropathy index at the 1997 follow-up examination increased with increasing initial dioxin in Ranch Hands. Ranch Hands in the high dioxin category also had an increased prevalence of polyneuropathy based on this index.

15.9.3. Polyneuropathy Prevalence Indicator

The prevalence of an abnormal polyneuropathy prevalence indicator, at the 1997 follow-up examination increased with increasing initial dioxin in Ranch Hands.

15.9.4. Polyneuropathy Severity Index

The prevalence of a moderate polyneuropathy severity index, at the 1997 follow-up examination was increased for Ranch Hands. Among Ranch Hands, the prevalence of a moderate polyneuropathy severity index at this examination increased with increasing initial dioxin and 1987 dioxin, and was increased for Ranch Hands in the high dioxin category.

15.9.5. Vibrotactile Threshold Measurement of the Great Toes

Among Ranch Hands exposed to heavy metals, the vibrotactile threshold level of the left and right great toes at the 1992 follow-up examination increased as initial dioxin increased. For Ranch Hands whose glucose levels were considered impaired (140 mg/dL ≤ 2-hour postprandial glucose < 200 mg/dL), the vibrotactile threshold level of the left great toe increased as initial dioxin increased. Ranch Hands in the background dioxin category who were heavy drinkers (>40 lifetime drink-years) had a greater average vibrotactile threshold measurement of the right great toe than Comparisons who were heavy drinkers. Ranch Hands in the high dioxin category who were nondrinkers had a greater average vibrotactile threshold measurement of the right great toe than Comparisons who were nondrinkers. For Ranch Hands who worked with heavy metals, the vibrotactile threshold level of the right great toe increased as 1987 dioxin levels increased. For Ranch Hands who worked with vibrating power equipment or tools, the vibrotactile threshold level of the left great toe increased as 1987 dioxin levels increased.

15.10. ARTICLE

15.10.1. Serum Dioxin and Peripheral Neuropathy in Veterans of Operation Ranch Hand

In a 2001 journal article, Michalek and colleagues (8) performed additional analysis on the study of polyneuropathy in AFHS veterans. Four indices to assess polyneuropathy were used:

- Any symmetrical peripheral abnormality
- Possible symmetric peripheral neuropathy
- Probable symmetric peripheral neuropathy
- Diagnosed peripheral neuropathy.

Any symmetrical peripheral abnormality was equivalent to the polyneuropathy prevalence indicator defined in Section 15.1.4. Diagnosed peripheral neuropathy was equivalent to the confirmed polyneuropathy index defined in Section 15.1.4. Possible symmetric peripheral neuropathy and probable symmetric peripheral neuropathy dealt with three outcomes first described in Section 15.1.4., that is,

- Both left and right Achilles reflexes were absent
- Reaction to a pinprick was abnormal on both the left and right feet
- Both left and right ankle vibrations were abnormal.

Possible symmetric peripheral neuropathy was defined to be present if one of the above three conditions held. Probable symmetric peripheral neuropathy was defined as present if at least two of the above three conditions held.

Data from the 1982, 1985, 1987, 1992, and 1997 examinations were analyzed using the categorized dioxin model. This model categorized Ranch Hands and Comparisons according to their estimated initial and 1987 dioxin levels into four categories: Comparisons, background Ranch Hands (1987 dioxin levels at or below 10 ppt), low Ranch Hands (1987 dioxin level greater than 10 ppt, initial dioxin level ≤ 94 ppt), and high Ranch Hands (1987 dioxin level greater than 10 ppt, initial dioxin level > 94 ppt).

The analysis of diagnosed peripheral neuropathy was restricted to data from the 1992 and the 1997 follow-up examinations because vibrotactile threshold data were collected only at these examinations. Nerve conduction velocities, measured at the 1982 baseline examination, also were analyzed, but no associations with dioxin were found. The analysis of bilateral vibrotactile abnormalities also showed no relations with dioxin.

A consistent increased risk of all indices of peripheral neuropathy among Ranch Hand veterans in the high dioxin category at the 1997 follow-up examination was found. An increased risk of diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, in Ranch Hand veterans in the high dioxin category at the 1992 follow-up examination also was seen. Restricting the analysis to the enlisted veterans did not alter these results. The authors stressed that cautious interpretation of these results was appropriate until the relation between pre-clinical diabetes mellitus and peripheral neuropathy had been further evaluated.

As a result of the article, the first three indicators of polyneuropathy described above—any symmetrical peripheral abnormality, possible symmetric peripheral neuropathy, and probable symmetric peripheral neuropathy—were evaluated for participants who attended the 2002 physical examination (7). No associations between dioxin and these indicators were observed.

15.11. CONCLUSION

Although many statistically significant findings were listed, many were just in isolated subpopulations; values were increased in one exam and then decreased in another; and findings rarely occurred in the same group in different examinations. An article on polyneuropathy showed an increased risk of all indices of peripheral neuropathy among Ranch Hand veterans in the high dioxin category at the 1997 follow-up examination. However, indicators of polyneuropathy - any symmetrical peripheral abnormality, possible symmetric peripheral neuropathy, and probable symmetric peripheral neuropathy - were evaluated for participants who attended the 2002 physical examination and no associations between dioxin and these indicators were observed. Thus, there was no evidence of a consistent relation between dioxin exposure and the neurologic system alteration in Ranch Hand veterans.

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16. PSYCHOLOGY ASSESSMENT

16.1. INTRODUCTION

A wide array of psychological abnormalities or impairments have been attributed or alleged to have occurred following exposure to chlorophenols, phenoxy herbicides, and dioxin. Many SEA veterans have expressed concern that exposure to herbicides had caused psychological and behavioral problems, as reflected by the Veterans Health Administration's Agent Orange Registry (1). Emotional illnesses or psychological abnormalities, however, are not recognized in the scientific community as primary clinical endpoints following exposure to chlorophenols, phenoxy herbicides, and dioxin. "Neurobehavioral effects" occasionally ascribed to such exposures have been, in fact, predominantly neurological symptoms for which causation is not disputed. Further, higher central nervous system functioning, in terms of cognitive skills and reactivity, may be temporarily or permanently impaired depending on the exposure and the ability to accurately measure the psychological changes.

At each of the six AFHS examinations (2-9), the questionnaire captured data on the occurrence of mental or emotional disorders. Each participant was asked whether he had a mental or emotional disorder since the date of his last interview. Medical record reviews confirmed reported conditions and identified any unreported conditions for each participant. As a result, psychological disorders were classified into four categories: psychoses, alcohol dependence, anxiety, and other neuroses for the 1982 and 1985 examinations. For the 1987 through 2002 examinations, psychological disorders were classified into five categories; drug dependence was added to the previous four categories. The category of disorders named "other neuroses" included the following conditions:

- Neurotic disorders, comprising hysteria, phobic disorders, obsessive-compulsive disorders, neurotic depression, neurasthenia, hypochondriasis, other neurotic disorders, and unspecified neurotic disorders
- Personality disorders
- Sexual deviations and disorders
- Nondependent abuse of drugs
- Physiological malfunction arising from mental factors
- Special symptoms or syndromes not elsewhere classified
- Acute reaction to stress
- Adjustment reaction
- Depressive disorder not elsewhere classified.

In addition to this verified history of psychological disorders, self-reported responses to questions assessing anger, anxiety, fatigue, and isolation were analyzed for the 1982 baseline examination. For the 1987 follow-up examination, each participant was asked a series of questions on whether he had a current or past problem with 12 different sleep disorders (10). Furthermore, a person was considered to have insomnia if he responded yes to having trouble falling asleep, waking up during the night, waking up too early and cannot go back to sleep. Also, an overall sleep disorder index was constructed, where a sleep disorder was defined as yes if a participant responded yes to any of the conditions. In addition, each person was asked the average number of hours slept per night.

The psychology assessment was based on the Cornell Index (11) and the Minnesota Multiphasic Personality Inventory (MMPI) (12) in 1982 and the Cornell Medical Index (CMI) (13) and the MMPI in 1985. Data from the Millon Clinical Multiaxial Inventory (MCMI) (14) were analyzed for the 1987 follow-up examination report. The Symptom Checklist-90-Revised (SCL-90-R) (15) was used at the 1987, 1992, 1997, and 2002 follow-up examinations. Central nervous system/cognitive functional testing was accomplished using a modified Halstead-Reitan Battery (16) in 1982 and 1985. Intelligence was measured by the Wechsler Adult Intelligence Scale (WAIS) (17) in 1982 and reading skills were tested by the reading subtest of the Wide Range Achievement Test (WRAT) (18) in 1982. Memory was tested by the Wechsler Memory Scale-Revised (19) at the 2002 follow-up examination. The following sections 16.1.1 through 16.1.5 describe the various tests.

16.1.1. Cornel Index

The Cornell Index was a subjective 10- to 15-minute self-administered inventory of neuropsychiatric symptoms and complaints.

16.1.2. CMI

The CMI was a self-administered instrument that consisted of 195 questions that were partitioned into 18 sections (A-R), with the number of questions within a section ranging from 6 to 23. Three scores were derived from the CMI: the total CMI score, an A-H area subscore, and an M-R subscore. The A-H subscore was a measure of the scatter of complaints, indicating a diffuse medical problem, although other interpretations were possible. The M-R subscore, which dealt with mood and feeling patterns, was a useful indicator of emotional ill health. The total CMI score was the number of affirmative responses on the entire CMI questionnaire.

16.1.3. MCMI

The MCMI, a self-administered test, comprised of 175 items and divided into 20 scales. Each of its 20 scales was constructed as an operational measure of a syndrome derived from a theory of personality and psychopathology. The MCMI was not designed to be a general personality instrument to be used for "normal" populations or for purposes other than diagnostic screening or clinical assessment. The 20 scales were organized into three broad categories to reflect distinctions between basic personality patterns, pathological personality disorders, and clinical symptom syndromes. Many of these scales were directly or indirectly correlated. Higher MCMI scores represented an adverse effect.

Eight scales from the MCMI focused on everyday ways of functioning that characterized participants even when they were not suffering acute symptom states. These eight scales were antisocial (aggressive), avoidant, compulsive (conforming), dependent (submissive), histrionic (gregarious), narcissistic, passive-aggressive (negativistic), and schizoid (asocial).

Three MCMI scales described patients who clearly evidence chronic or periodically severe pathology in the overall structure of personality. These scales are borderline (cycloid), paranoid, and schizotypal (schizoid).

Nine scales from the MCMI measured reactive disorders, often precipitated by external events that were of substantially briefer duration than the personality disorders. Six scales—alcohol abuse, anxiety, drug abuse, dysthymic, hypomanic, and somatoform—represented disorders of moderate severity. The other three scales—psychotic delusions, psychotic depression, and psychotic thinking—reflected disorders of marked severity.

16.1.4. MMPI

The MMPI was a self-administered test that comprised 566 questions on various aspects of behavior and personality. The results of the MMPI were numerical scores for 14 scales. The scales were anxiety (psychasthenia), consistency, defensiveness, denial, depression, hypochondria, hysteria, mania/hypomania, masculinity/femininity, paranoia, psychopathic/deviate, schizophrenia, social introversion, and validity.

16.1.5. SCL-90-R

The SCL-90-R was a self-administered test taken by participants at the 1987, 1992, 1997, and 2002 follow-up examinations. Twelve variables were derived from the SCL-90-R, which comprised nine primary symptom categories and three global indices of distress. The function of the three global measures of the SCL-90-R—the global severity index, the positive symptom distress index, and the positive symptom total—was to communicate in a single score the level or depth of the individual's psychopathology. A short description of each of the primary symptom categories and global indices of distress, which was taken from the SCL-90-R reference manual, is given below for each category/indices where an adverse finding for Ranch Hands was found.

The SCL-90-R anxiety dimension was a set of signs and symptoms that were associated clinically with high levels of manifest anxiety. General signs such as nervousness, tension, and trembling were included in the definition, as were panic attacks and feelings of terror. Cognitive components involved feelings of apprehension and dread, and some of the somatic correlates of anxiety also were included as dimensional components. The symptoms comprising the anxiety dimension were experiencing nervousness or shakiness inside, trembling, being suddenly scared for no reason, feeling fearful, experiencing heart pounding or racing, feeling tense and keyed up, having spells of terror and panic, feeling so restless you couldn't sit still, feeling that something bad was going to happen, and experiencing frightening thoughts and images.

The symptoms of the depression dimension reflected a broad range of the manifestations of clinical depression. Symptoms of dysphoric mood and affect were represented, as were signs of withdrawal of life interest, lack of motivation, and loss of vital energy. In addition, feelings of hopelessness, thoughts of suicide, and other cognitive and somatic correlates of depression were included. The symptoms comprising the depression dimension were losing sexual interest or pleasure, feeling low in energy or a slowing down, thinking of ending your life, crying easily, feeling trapped or caught, blaming yourself for things, feeling lonely, feeling blue, worrying too much about things, feeling no interest in things, feeling hopeless about the future, feeling everything was an effort, and feeling worthless.

The hostility dimension reflected thoughts, feelings, or actions that were characteristic expressions of anger. The items comprising the hostility dimension were selected to measure the three modes of manifestation (i.e., thoughts, feelings, actions) and reflected qualities such as aggression, irritability, rage, and resentment. The dimension's symptoms were feeling easily annoyed or irritated; having uncontrollable temper outbursts; having urges to beat, injure, or harm someone; having urges to break or smash things; getting into frequent arguments; and shouting or throwing things.

The obsessive-compulsive dimension reflected symptoms that were highly identified with the standard clinical syndrome of the same name. This measure focused on thoughts, impulses, and actions that were experienced as unremitting and irresistible by the individual and inconsistent with the individual's own beliefs about what was desirable or reasonable. Behaviors and experiences of more general cognitive performance attenuation also were included in this measure. The symptoms comprising the obsessive-compulsive dimension were experiencing repeated unpleasant thoughts that won't leave the mind, having trouble remembering things, worrying about sloppiness or carelessness, feeling blocked in getting things done, having to do things very slowly to ensure correctness, having to check and double-check what was

done, having difficulty making decisions, having mind blanks, having trouble concentrating, and having to repeat the same actions (e.g., touching, counting, washing).

The paranoid ideation dimension represented paranoid behavior fundamentally as a disordered mode of thinking. The cardinal characteristics of projective thought, hostility, suspiciousness, grandiosity, centrality, fear of loss of autonomy, and delusions were viewed as primary reflections of this disorder; item selection was oriented toward representing this conceptualization. The symptoms comprising the paranoid ideation dimension were feeling others were to blame for most of your troubles, feeling that most people could not be trusted, feeling that you were watched or talked about by others, having ideas and beliefs that others do not share, not receiving proper credit from others for your achievements, and feeling that people would take advantage of you if you let them.

The psychoticism scale was developed in a fashion to represent the construct as a continuous dimension of human experience. Items indicative of a withdrawn, isolated, schizoid lifestyle were included, as were Schneiderian first-rank symptoms of schizophrenia, such as hallucinations and thought broadcasting. The symptoms comprising the psychoticism dimension were having the idea that someone else can control your thoughts, hearing voices that other people do not hear, believing that other people were aware of your private thoughts, having thoughts that were not your own, feeling lonely even when you were with people, having thoughts about sex that were continuously bothersome, believing that you should be punished for your sins, thinking that something serious was wrong with your body, never feeling close to another person, and thinking that something was wrong with your mind.

The somatization dimension reflected distress arising from perceptions of bodily dysfunction. Complaints focusing on cardiovascular, gastrointestinal, respiratory, and other systems with strong autonomic mediation were included. Headaches, pain, and discomfort of the gross musculature and additional somatic equivalents of anxiety were components of the definition. These symptoms and signs had all been demonstrated to have high prevalence in disorders demonstrated to have a functional etiology, although all may be reflections of true physical disease. The symptoms comprising the somatization dimension were headaches, faintness or dizziness, pains in heart or chest, pains in lower back, nausea or upset stomach, soreness of muscles, trouble getting breath, hot or cold spells, numbness or tingling in parts of body, lump in throat, weakness in parts of body, and heavy feelings in arms or legs.

The global severity index represented the best single indicator of the current level or depth of the disorder and should be used in most instances in which a single summary measure was required. The global severity index combined information on numbers of symptoms and intensity of perceived distress.

16.1.6. Articles

Two journal articles were published by AFHS staff and their colleagues based on the psychological data collected at the AFHS examinations:

- Serum dioxin and psychological functioning in U.S. Air Force veterans of the Vietnam War (20)
- Serum dioxin and cognitive functioning in veterans of Operation Ranch Hand (21).

16.1.7. IOM Veterans and Agent Orange Report

In the IOM 2004 *Veterans and Agent Orange* update (22), the committee concluded that there was "inadequate or insufficient" evidence of an association between exposure to certain herbicides used in Vietnam and cognitive or neuropsychiatric disorders.

The following chart lists the variables that were analyzed for the psychology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Alcohol Dependence	X	X	X	X	**X**	X	X
Anxiety	X	X	X	X	X	X	X
Cornell Index (Overall and 10 Scales):	**X**						
Cornell Medical Index (3 Scores)		**X**					
Drug Dependence			X	X	X	X	X
Halstead-Reitan Battery Impairment Index	X	X					
MCMI (20 Scales)			**X**	**X**			
MMPI (14 Scales)	**X**	**X**					
Other Neuroses	X	X	X	**X**	**X**	**X**	X
Psychoses	X	X	X	X	X	X	X
Questionnaire Indices (Anger, Anxiety, Depression [Severity], Erosion, Fatigue, Isolation)	**X**						
SCL-90-R (12 Scales)			**X**	**X**	**X**	X	X
Sleep Disorders:							
Abnormal Movement/Activity During the Night			X	X			
Average Sleep Each Night			X	**X**			
Frightening Dreams			X	**X**			
Great or Disabling Fatigue During the Day			X	X			
Insomnia			X	X			
Involuntarily Falling Asleep During the Day			X	X			
Overall Sleep Disorder Index			X	X			
Sleep Problems Requiring Medication			X	X			
Sleepwalking			X	X			
Snore Loudly in All Sleeping Positions			X	X			
Talking in Sleep			X	X			
Trouble Falling Asleep			X	X			
Waking Up During the Night			X	X			
Waking Up Too Early and Can't Go Back to Sleep			X	X			
Waking Up Unrefreshed			X	X			
Wechsler Adult Intelligence Scale (Verbal, Performance, and Full Scale)	X						
WMS-R Memory Tests (5 Scores)							X

16.2. ALCOHOL DEPENDENCE

At the 1992 follow-up examination, married enlisted groundcrew Ranch Hands showed a higher prevalence of alcohol dependence after service in SEA than married enlisted groundcrew Comparisons.

16.3. CORNELL INDEX

Among those participants with at most a high school education, Ranch Hands had a greater average total Cornell index score than Comparisons.

16.4. CORNELL MEDICAL INDEX (CMI)

Ranch Hands had a higher average A-H area subscore than Comparisons. Among those participants with at most a high school education, Ranch Hands had a higher average total CMI score than Comparisons.

16.5. MILLON CLINICAL MULTIAXIAL INVENTORY (MCMI)

16.5.1. Antisocial

Ranch Hands in the background dioxin category who were heavy drinkers (more than four drinks per day) had a higher average MCMI antisocial score than Comparisons who were heavy drinkers. In addition, Ranch Hands in the low dioxin category who were light drinkers (no more than one drink per day) had a higher average MCMI antisocial score than Comparisons who were light drinkers.

16.5.2. Avoidant

The MCMI avoidant score increased as initial dioxin increased. This relation between the MCMI avoidant score and initial dioxin was present when all Ranch Hands were examined and when analysis was restricted to college-educated Ranch Hands. In addition to the relation with initial dioxin, an association between the MCMI avoidant score and 1987 dioxin levels was observed in Ranch Hands with earlier tours of duty.

16.5.3. Compulsive

For participants who were heavy drinkers, Ranch Hands had a higher average MCMI compulsive score than Comparisons.

16.5.4. Dependent

The MCMI dependent score in Ranch Hands increased as initial dioxin increased and as 1987 dioxin levels increased in Ranch Hands with earlier tours of duty.

16.5.5. Histrionic

The MCMI histrionic score increased as initial dioxin increased in Black Ranch Hands with later tours of duty.

16.5.6. Narcissistic

Ranch Hands had a higher average MCMI narcissistic score than Comparisons.

16.5.7. Passive-aggressive

Among participants with at most a high school education, Ranch Hands had a higher average MCMI passive-aggressive score than Comparisons. Younger Ranch Hands in the background dioxin category also had a higher average MCMI passive-aggressive score than younger Comparisons.

16.5.8. Schizoid

Among nondrinkers and moderate drinkers (no more than 40 lifetime drink-years), the MCMI schizoid score in Ranch Hands with earlier tours of duty increased as 1987 dioxin increased. The MCMI schizoid score also increased as initial dioxin in Ranch Hands increased.

16.5.9. Borderline

The MCMI borderline score increased as initial dioxin increased in college-educated Ranch Hands.

16.5.10. Paranoid

Ranch Hands had a higher average MCMI paranoid score than Comparisons.

16.5.11. Schizotypal

The MCMI schizotypal score increased as initial dioxin in Ranch Hands increased and as 1987 dioxin increased in Ranch Hands with earlier tours of duty.

16.5.12. Alcohol Abuse

The average MCMI alcohol abuse score for Black Ranch Hands in the background and high dioxin categories was higher than the average MCMI alcohol abuse score for Black Comparisons.

16.5.13. Anxiety

Black Ranch Hands had a higher average MCMI anxiety score than Black Comparisons. Black Ranch Hands in the background dioxin category also had a higher average MCMI anxiety score than Black Comparisons. An association between the MCMI anxiety score and initial dioxin was observed in non-Black Ranch Hands. As initial dioxin increased, the MCMI anxiety score increased for non-Black Ranch Hands.

16.5.14. Dysthymia

The MCMI dysthymia score in non-Black Ranch Hands increased as initial dioxin increased.

16.5.15. Hypomania

The MCMI hypomania score in Black Ranch Hands increased as initial dioxin increased. The average MCMI hypomania score also was increased in Black Ranch Hands in the high dioxin category relative to Black Comparisons.

16.5.16. Somatoform

The MCMI somatoform score increased as 1987 dioxin levels in Ranch Hands with later tours of duty increased and as initial dioxin in Ranch Hands increased.

16.5.17. Psychotic Depression

The MCMI psychotic depression score increased as initial dioxin in Ranch Hands increased and as 1987 dioxin levels in Ranch Hands with earlier tours of duty increased.

16.6. MINNESOTA MULTIPHASIC PERSONALITY INVENTORY (MMPI)

16.6.1. Depression

Ranch Hands had a greater prevalence of high scores on the MMPI depression scale than Comparisons at the 1982 baseline examination.

16.6.2. Hypochondria

Ranch Hands had a greater prevalence of high scores on the MMPI hypochondria scale than Comparisons at the 1982 baseline examination.

16.6.3. Hysteria

Ranch Hands had a greater prevalence of high scores on the MMPI hysteria scale than Comparisons at the 1982 baseline examination.

16.6.4. Mania/Hypomania

Among participants with at most a high school education, Ranch Hands had a higher average MMPI mania/hypomania score than Comparisons at the 1982 baseline examination.

16.6.5. Masculinity/Femininity

Among participants with at most a high school education, Ranch Hands had a higher average MMPI masculinity/femininity score than Comparisons at the 1982 baseline examination.

16.6.6. Paranoia

Older Ranch Hands had a greater prevalence of abnormal scores on the MMPI paranoia scale than older Comparisons at the 1985 follow-up examination.

16.6.7. Schizophrenia

Ranch Hands with at most a high school education had a greater prevalence of abnormal scores on the MMPI schizophrenia scale at the 1985 follow-up examination than Comparisons with at most a high school education.

16.6.8. Social Introversion

Among participants with at most a high school education, Ranch Hands had a higher average MMPI social introversion score at the 1982 baseline examination than Comparisons. Ranch Hands had a greater prevalence of abnormal scores on the MMPI social introversion scale at the 1985 follow-up examination than Comparisons.

16.7. OTHER NEUROSES

Based on data at the 1987 follow-up examination, Ranch Hands in the low dioxin category exhibited a higher prevalence of other neuroses than Comparisons after service in SEA.

Among enlisted groundcrew personnel, participants with at most a high school education, and participants in higher income households, Ranch Hands showed a higher prevalence of other neuroses at the 1992 follow-up examination than Comparisons after service in SEA. Among participants with at most a high school education, Ranch Hands in the background and low dioxin categories also showed a higher prevalence of other neuroses than Comparisons after service in SEA. Among participants in higher income households, Ranch Hands in the high dioxin category showed a greater prevalence of other neuroses than Comparisons after service in SEA.

Based on data collected at the 1997 follow-up examination, Ranch Hand enlisted groundcrew had a higher prevalence of other neuroses than Comparison enlisted groundcrew after service in SEA. Ranch Hands in the low dioxin category also exhibited a higher prevalence of other neuroses than Comparisons

after service in SEA. Based on data collected at the 1997 follow-up examination, further analysis of other neuroses by the individual categories provided above showed no predominance of any one category (8).

16.8. ANGER, ANXIETY, FATIGUE, AND ISOLATION

Questionnaire response from the 1982 baseline examination concerning anger, anxiety, fatigue, and isolation showed higher levels of these parameters for Ranch Hands than Comparisons in participants with at most a high school education, but not in participants with a college education.

16.9. SYMPTOM CHECKLIST-90-REVISED (SCL-90-R)

16.9.1. Anxiety

Based on data from the 1987 follow-up examination, the prevalence of high SCL-90-R anxiety scores increased as 1987 dioxin increased in Ranch Hands with earlier tours of duty. This positive association between SCL-90-R anxiety and 1987 dioxin also was seen at the 1992 follow-up examination for participants who drank, on average, at most one drink per day.

16.9.2. Depression

For moderate lifetime Ranch Hand drinkers (between 0 and 40 lifetime drink-years), the prevalence of high SCL-90-R depression scores at the 1992 follow-up examination increased as initial dioxin increased. Among Ranch Hands in higher income households and Black Ranch Hands, the prevalence of high SCL-90-R depression scores also increased as 1987 dioxin increased.

16.9.3. Hostility

At the 1992 follow-up examination, for enlisted groundcrew who had at most a high school education, Ranch Hands had a greater prevalence of high SCL-90-R hostility scores than Comparisons.

16.9.4. Obsessive-compulsive Behavior

Ranch Hands had a greater prevalence of high SCL-90-R obsessive-compulsive scores than Comparisons at the 1992 follow-up examination. In relation to dioxin levels, this difference was seen for Ranch Hands in the background dioxin category. An interaction between current alcohol use, household income, and 1987 dioxin also was observed in the analysis of SCL-90-R obsessive-compulsive scores.

16.9.5. Paranoid Ideation

At the 1992 follow-up examination, for non-Black enlisted personnel, Ranch Hands had a greater prevalence of high SCL-90-R paranoid ideation scores than Comparisons. Ranch Hands in the background dioxin category also had a greater prevalence of high SCL-90-R paranoid ideation scores than Comparisons.

16.9.6. Psychoticism

Among moderate and heavy current drinkers (greater than one drink per day, on average), Ranch Hands in the background dioxin category had a greater prevalence of high SCL-90-R psychoticism scores than Comparisons at the 1992 follow-up examination.

16.9.7. Somatization

Ranch Hands with at most a high school education had a greater prevalence of high SCL-90-R somatization scores than Comparisons with at most a high school education at the 1987 follow-up examination.

At the 1992 follow-up examination, more Ranch Hands than Comparisons had high SCL-90-R somatization scores. In particular, the increase appeared to be for Ranch Hands with background dioxin levels relative to Comparisons. Among Ranch Hands with a college education, the prevalence of high SCL-90-R somatization scores at the 1992 follow-up examination increased as 1987 dioxin increased.

16.9.8. Global Severity Index

Among non-Black Ranch Hands with earlier tours of duty at the 1987 follow-up examination, the prevalence of high SCL-90-R global severity index scores increased as 1987 dioxin increased.

Ranch Hands had a higher prevalence of high SCL-90-R global severity index scores than Comparisons at the 1992 follow-up examination. Among Ranch Hands who drank less than one alcoholic drink per day, the prevalence of high SCL-90-R global severity index scores at the 1992 follow-up examination increased with both initial and 1987 dioxin. In addition, among Ranch Hands in higher income households, the prevalence of high SCL-90-R global severity index scores at the 1992 follow-up examination increased as 1987 dioxin increased.

16.10. SLEEP DISORDERS

Based on data collected at the 1987 follow-up examination, Ranch Hands in the high dioxin category had a greater prevalence of past or present problems with frightening dreams. In addition, as 1987 dioxin increased for Ranch Hands with later tours of duty, the prevalence of past or present problems with frightening dreams increased.

Based on information reported by participants at the 1987 follow-up examination, the average number of hours of sleep each night decreased as 1987 dioxin increased among Black participants with earlier tours of duty.

16.11. ARTICLES

16.11.1. Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam War

A 2003 journal article analyzed the association of dioxin and psychological functioning for all AFHS participants with a dioxin level (for Comparisons less than 10 ppt) and who had results for the MMPI administered at the 1982 and 1985 examinations and the MCMI administered at the 1987 and 1992 follow-up examinations (20). Only Ranch Hands in the background dioxin category were more likely to have elevated MCMI scale scores based on data from the 1992 follow-up examination. These elevations were primarily in the basic personality patterns. Ranch Hand veterans in the low and the high dioxin categories were similar to Comparisons in analysis of both the 1987 and 1992 follow-up examination data.

Few associations between dioxin levels and clinical elevations on the MMPI were seen based on data collected at the 1982 baseline examination. The direction and patterns of the associations were inconsistent. Ranch Hand veterans in the high dioxin category showed some difficulties in anxiety, somatization, depression, and a denial of psychological factors. Ranch Hand veterans with background

levels also showed indications of emotional distress, primarily in emotional numbing and lability; a guarded, suspicious, and withdrawn style of relating to others; and unusual thoughts or behaviors.

No positive associations between dioxin level and clinical elevations on the MMPI scales were observed based on data collected at the 1985 follow-up examination. No association between dioxin and post-traumatic stress disorder, as measured from questions on the MMPI, was observed at either the 1982 or 1985 AFHS examinations.

16.11.2. Serum Dioxin and Cognitive Functioning in Veterans of Operation Ranch Hand

The association of cognitive functioning in relation to dioxin levels was analyzed in a 2001 journal article (11). To assess cognitive functioning the Halstead–Reitan Battery (16), the WAIS-Revised (17), the Wechsler Memory Scale (21), and the WRAT (18) were administered at the 1982 baseline examination. Those individuals that took the cognitive testing and had dioxin levels drawn either at the 1987 or 1992 examinations were included in the analyzes. Results were adjusted for multiple variables, such as military occupation, age, race, marital status, psychotropic medication use, and psychiatric diagnoses.

The results of this study suggested that, although there were no global decrements in cognitive functioning associated with dioxin exposure among Vietnam veterans, there were specific decrements involving verbal and tactual memory functioning. Based on the Wechsler Memory Scale administered at the 1982 baseline examination, there were decrements in tasks involving verbal memory functioning in Ranch Hands with the highest dioxin levels relative to Comparisons. The same pattern also was found in Ranch Hand enlisted personnel with reported skin exposure to herbicides, relative to enlisted Comparison personnel. The differences were relatively small, however, and of uncertain clinical meaning.

Analysis of the Halstead impairment index as derived from the Halstead-Reitan Battery, which was a crude measure for categorizing brain damage, showed that Ranch Hand veterans with low dioxin exposure were more likely than Comparison veterans to be rated as severely impaired. The number of veterans categorized as severely impaired, however, was small (n=64), and the average impairment score for Ranch Hand veterans was not different from Comparisons.

Ranch Hand veterans with low dioxin levels showed slower motor speed, as measured by the Halstead-Reitan finger-tapping test on both the dominant and the nondominant hand. Ranch Hand veterans with background dioxin levels showed decreased motor strength, as measured by the Halstead-Reitan grip strength test with the nondominant hand only. These results were of small and uncertain clinical meaning, with no clear dose-response pattern.

As a result of this report, a revised version of the Wechsler Memory Scale (23) was administered at the 2002 follow-up examination. No differences in the memory scale between groups were found, and no associations between the memory scales and dioxin were observed.

16.12. CONCLUSIONS

The 1982 baseline examination showed more differences between Ranch Hands and Comparisons (primarily those participants with at most a high school education) in subjective measurements rather than objective measurements. When multiple test instruments that measured similar variables were used, such as the SCL-90-R and the MCMI at the 1987 follow-up examination, there appeared to be a lack of consistency in the outcomes. Although differences between groups and associations with dioxin were seen in the psychological tests performed, they were sporadic, rarely seen in the high dioxin category and inconsistent across examinations.

The articles also showed no global decrements in cognitive and psychological functioning associated with dioxin exposure. The only finding in the highest dioxin levels was in tasks involving verbal memory functioning at the 1982 baseline examination, and these differences were not observed at the 2002 follow-up examination.

In summary, there does not appear to be any clear evidence of disorders or syndromes that can be associated with exposure to herbicides and dioxin.

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17. PULMONARY ASSESSMENT

17.1. INTRODUCTION

Pulmonary dysfunction and overt pulmonary disease are not recognized clinical entities resulting from exposure to chlorophenols, phenoxy herbicides, or dioxin. Acute exposure to chlorophenols, phenoxy herbicides, and dioxin has caused the traditional acute symptoms of cough, nasal and lung irritation, shortness of breath, and occasionally, bronchitis. These acute effects and the high likelihood of inhalation exposure to herbicides among the Operation Ranch Hand personnel in Vietnam prompted the evaluation of the pulmonary status of AFHS participants.

Analyses were performed to assess the pulmonary function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). In the questionnaire each study participant was asked whether he had ever experienced asthma, bronchitis, pleurisy, pneumonia, or tuberculosis. Medical records reviews were conducted to confirm reported pulmonary conditions and to identify any unreported conditions for each participant. Asthma, bronchitis and pneumonia were analyzed at the 1985 through 2002 physical examinations. Pleurisy and tuberculosis were analyzed at the 1985 and 1987 physical examinations.

Part of the pulmonary assessment was based on the results of the physical examination of the thorax and lungs. For the 1985 through 2002 follow-up examinations a composite variable, 'thorax and lung abnormality', was constructed based on the presence or absence of asymmetrical expansion, hyperresonance, dullness, wheezes, rales, or chronic obstructive pulmonary disease, as well as the physician's assessment of the abnormality. The individual conditions of asymmetrical expansion, hyperresonance, dullness, wheezes, and rales were also analyzed for the 1985 and 1987 follow-up examinations.

At the 1985 through 2002 physical examinations, the assessment of the laboratory examination data included the interpretation of pulmonary abnormalities detected on a routine chest x-ray film. This variable was coded as normal or abnormal. The assessment also included the analysis of pulmonary physiological data collected during the physical examination employing standard spirometry techniques. Numerous indices were derived including forced vital capacity (FVC); a measurement of the amount of air in liters expelled from maximum inspiration to full expiration; forced expiratory volume in 1 second (FEV_1) in liters; an index derived from the FVC that quantified the amount of air expelled in 1 second; FEV in 2 seconds (FEV_2); FEV in 3 seconds (FEV_3); and forced expiratory flow maximum. The values used for these variables were the percentages of predicted values rather than the actual volume or flow rate. In addition, the ratio of observed FEV_1 to observed FVC was calculated as an index reflective of obstructive airway disease. For these indices, lower values indicated greater compromise in lung function. The FVC and the FEV_1 were based on the percent of predicted values, and the predicted values were adjusted for age and height. FEV_1, FVC, and observed FEV_1 to observed FVC ratio were analyzed at the 1982, 1987, 1992, 1997, and 2002 follow-up physical examinations. At the 1987, 1992, 1997, and 2002 physical examinations loss of vital capacity and obstructive abnormality were classified by the physician as none, mild, moderate, or severe. Analyses were adjusted for age, race, military occupation, and measures of current and lifetime smoking.

The IOM *Veterans and Agent Orange* reports, including the 2004 update (8), concluded that there was "inadequate or insufficient" evidence to determine the existence of an association between exposure to certain herbicides used in the Vietnam War and nonmalignant respiratory disorders.

The following chart lists the variables that were analyzed for the pulmonary assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Asymmetrical Expansion		X	X	X			
Asthma		X	X	**X**	X	X	X
Bronchitis		X	X	X	**X**	X	X
Dullness		X	X	X			
FEV_1	X		**X**	**X**	X	X	X
FEV_2			X				
FEV_3			X				
Forced Expiratory Flow Maximum			X	X			
FVC	X		X	**X**	**X**	X	**X**
Hyperresonance		X	**X**	**X**			
Observed FEV_1 to Observed FVC Ratio	X		X	**X**	**X**	X	X
Obstructive Abnormality			X	**X**	**X**	**X**	X
Pleurisy		**X**	X	X			
Pneumonia		X	X	X	X	X	**X**
Rales		X	X	**X**			
Thorax and Lung Abnormality		X	X	**X**	**X**	X	X
Tuberculosis		X	X	X			
Vital Capacity, Loss			X	**X**	**X**	X	X
Wheezes		X	X	**X**			
X-ray Interpretation		X	X	X	X	**X**	X

17.2. ASTHMA

Ranch Hands in the background dioxin category had a higher prevalence of asthma after service in SEA than Comparisons at the time of the 1987 follow-up examination.

17.3. BRONCHITIS

In the enlisted flyer cohort and the background dioxin category, Ranch Hands had a higher prevalence of bronchitis after service in SEA than Comparisons in the analysis of the 1992 follow-up examination data.

17.4. FEV_1

For the analysis of data from the 1987 follow-up examination, the average FEV_1 was smaller in older Ranch Hands than in older Comparisons. Among participants who had never smoked and former smokers, Ranch Hands in the high dioxin category had a smaller average FEV_1 than Comparisons. FEV_1 levels in 1987 decreased as initial and 1987 dioxin levels increased.

17.5. FVC

Similar interaction patterns to those seen for FEV_1 were observed with average FVC levels at the 1987 follow-up examination. Among participants who had never smoked and former smokers, Ranch Hands in

the high dioxin category had a smaller average FVC than Comparisons. FVC levels in 1987 decreased as initial and 1987 dioxin levels increased.

FVC, as measured at the 1992 follow-up examination, decreased as initial dioxin increased. Average FVC levels at the 2002 follow-up examination were smaller for Ranch Hands in the low dioxin category than for Comparisons.

17.6. HYPERRESONANCE

The prevalence of hyperresonance was elevated among Ranch Hand enlisted flyers at the 1987 follow-up examination. In addition, as 1987 dioxin levels increased in Ranch Hands with early tours of duty, the prevalence of hyperresonance in 1987 increased.

17.7. OBSERVED FEV_1 TO OBSERVED FVC RATIO

Ranch Hands in the background dioxin category had a smaller average ratio of FEV_1 to FVC than Comparisons at the 1987 follow-up examination. This pattern also was observed in older Ranch Hands at the 1992 follow-up examination.

17.8. OBSTRUCTIVE ABNORMALITY

The occurrence of a mild obstructive abnormality was increased for Ranch Hands in the background dioxin category at the 1987 follow-up examination. This same increase was observed at the 1992 follow-up examination for Ranch Hand smokers who were heavy smokers. At the 1997 follow-up examination, the occurrence of a mild obstructive abnormality was increased for Ranch Hand officers.

17.9. PLEURISY

The prevalence of pleurisy after service in SEA was increased among Ranch Hands with a moderate lifetime cigarette smoking history (more than 0 pack-years but no more than 10 pack-years) at the time of the 1985 follow-up examination.

17.10. PNEUMONIA

The prevalence of pneumonia after service in SEA was increased among Ranch Hand enlisted flyers at the 2002 physical examination.

17.11. RALES

The prevalence of rales was increased for Ranch Hands in the high dioxin category at the 1987 follow-up examination.

17.12. THORAX AND LUNG ABNORMALITY

The occurrence of thorax and lung abnormalities identified at the 1987 follow-up examination increased with initial and 1987 dioxin levels. At the 1992 follow-up examination, Ranch Hands had a greater prevalence of thorax and lung abnormalities, primarily among enlisted flyers. Ranch Hands in the background dioxin category also had a greater prevalence of thorax and lung abnormalities than Comparisons at this examination.

17.13. VITAL CAPACITY, LOSS

At the 1987 follow-up examination, more Ranch Hands with high levels of 1987 dioxin and later tours of duty had mild losses of vital capacity than did Ranch Hands with low levels of 1987 dioxin and later tours of duty. More Ranch Hands with high levels of 1987 dioxin had mild losses of vital capacity than did Comparisons. In addition, as initial dioxin increased, the risk of a mild loss of vital capacity increased.

At the 1992 follow-up examination, the occurrence of a mild loss of vital capacity in nonsmokers increased as 1987 dioxin increased.

17.14. WHEEZES

The prevalence of wheezes increased as initial dioxin increased for the serum dioxin analysis of the 1987 follow-up report. Analysis in this report also showed the prevalence of wheezes increased as 1987 dioxin increased among older Ranch Hand participants with later tours of duty.

17.15. X-RAY INTERPRETATION

Ranch Hands in the background dioxin category had a higher prevalence of abnormal chest x-ray interpretations than Comparisons in the analysis of the 1997 follow-up examination.

17.16. CONCLUSION

Patterns that might be expected if there were dioxin or herbicide effects on the pulmonary function, namely consistent results across examinations, an adverse health effect for Ranch Hands or Ranch Hand enlisted groundcrew, and adverse effects to Ranch Hands in the high dioxin category, were not evident. Sporadic and isolated effects were present in many of the endpoints examined, but there was no consistent evidence to suggest that herbicide or dioxin exposure was associated with ill effects on respiratory health.

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18. RENAL ASSESSMENT

18.1. INTRODUCTION

Renal (kidney) dysfunction and overt renal disease were not considered major clinical sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin. Both 2,4-D and 2,4,5-T, however, are excreted by the kidney as both metabolized and unmetabolized compounds. Therefore, it is consistent that acute renal dysfunction has been reported following acute, high-dose exposure to phenoxy herbicides and dioxin.

Analyses were performed to assess the renal function of AFHS participants at the 1982, 1985, 1987, 1992, and 2002 examinations (1-6); renal was not analyzed at the 1997 physical examination. The renal assessment was based on laboratory data collected at the physical examination, as well as a verified lifetime history of kidney stones and kidney disease, as reported by the participant and subsequently verified by a medical records review. Statistical analysis included adjustment for relevant risk and demographic factors.

In the questionnaire each AFHS participant was asked whether he had ever experienced kidney trouble or kidney stones. A medical records review was accomplished to confirm reported problems with kidney function and to identify any unreported kidney problems. Predominate conditions for past kidney disease included kidney stones, unspecified disorders of the kidney and ureter, and nonspecific findings on the examination of the urine. History of kidney stones was only analyzed at the 2002 physical examination

Renal variables were quantified by laboratory tests to assess renal system function. Urinary protein was analyzed for the 1982, 1985, 1987, and 2002 physical examinations and urine specific gravity was analyzed for the 1982-1992, and 2002 physical examinations. Both were determined by accepted dipstick methods. Urinary occult blood and urinary WBC count were measured by high-powered microscopic examination for the five physical examinations. Serum creatinine was analyzed in 1992 and 2002; urinary microalbumin to creatinine ratio was analyzed in 2002; and blood urea nitrogen (BUN) was analyzed at the 1982, 1985 and 1987 physical examinations. At the 1992 physical examination only, kidney, urethra and bladder (KUB) x-ray results were analyzed for kidney stones. Creatinine clearance was analyzed at the 1982 and 2002 follow-up physical examinations. At the 1982 examination only, a renal abnormality episode score consisting of BUN, creatinine clearance, urinary occult blood, urinary WBCs and urinary protein was analyzed. It was considered abnormal if one of the measurements was abnormal.

The IOM Veterans and Agent Orange reports through 2004 did not address non-cancerous renal disorders.

The following chart lists the variables that were analyzed for the renal assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Blood Urea Nitrogen	X	X	X	X		Analysis not performed	X
Creatinine, Serum					**X**		X
Creatinine Clearance	X						X
Kidney Disease, History	**X**	X	X	X	X		X
Kidney Stones, History							X
Kidney Stones from Kidney, Urethra, and Bladder X-ray Assessment					X		
Microalbumin to Creatinine Ratio, Urinary							X
Occult Blood, Urinary	X	X	**X**	**X**	**X**		X
Protein, Urinary	X	**X**	X		**X**		X
Renal Abnormalities, Composite (Blood Urea Nitrogen, Creatinine Clearance, Urinary Occult Blood, Urinary White Blood Cells, Urinary Protein)	X						
Specific Gravity, Urine	X	**X**	X	X	**X**		X
White Blood Cells, Urinary	X	**X**	X	X	**X**		X

18.2. CREATININE, SERUM

For participants whose glucose levels were considered impaired (140 mg/dL ≤ 2-hour postprandial glucose < 200 mg/dL), Ranch Hands had a higher average serum creatinine level at the 1992 follow-up examination than Comparisons.

18.3. KIDNEY DISEASE, HISTORY

Answers to the 1982 baseline questionnaire question "Have you ever had kidney disease?" showed that Ranch Hands self-reported more kidney disease than Comparisons.

18.4. OCCULT BLOOD, URINARY

Black Ranch Hands exhibited a greater percentage of abnormal levels of urinary occult blood (greater than 2 cells per high-powered field) than Black Comparisons at the 1987 follow-up examination. The percentage of abnormal levels of urinary occult blood also increased with increasing initial dioxin at the 1987 follow-up examination. At the 1992 follow-up examination, the prevalence of abnormal levels of urinary occult blood increased with categorized dioxin and 1987 dioxin.

18.5. PROTEIN, URINARY

For participants whose glucose levels were considered normal (2-hour postprandial glucose < 140 mg/dL), more Ranch Hands had urinary protein present at the 1985 follow-up examination than did Comparisons.

For participants whose glucose levels were considered impaired the percentage of Ranch Hands who had urinary protein present at the 1992 follow-up examination increased as the level of 1987 dioxin increased.

18.6. SPECIFIC GRAVITY, URINE

Average urine specific gravity levels were greater for non-Black Ranch Hand enlisted groundcrew than for non-Black Comparison enlisted groundcrew at the 1985 follow-up examination. Urine specific gravity levels among older participants increased as initial dioxin increased at the 1992 follow-up examination. Urine specific gravity levels at the 1992 follow-up examination also increased as 1987 dioxin increased.

18.7. WHITE BLOOD CELLS, URINARY

Younger non-Black Ranch Hands exhibited a greater percentage of abnormal levels of urinary WBCs (greater than 2 cells per high-powered field) than younger non-Black Comparisons at the 1985 follow-up examination. At the 1992 follow-up examination, the prevalence of abnormal levels of urinary WBCs was greater for Ranch Hand enlisted groundcrew than for Comparison enlisted groundcrew.

18.8. CONCLUSION

The AFHS evaluated renal disorders based on medical histories and standard laboratory measures. Throughout the AFHS, the findings of adverse effects or associations with dioxin that were observed appeared to be sporadic and inconsistent across examinations. Many of the relations that were found were present only in subpopulations with no biological basis. The results of the renal assessment indicated there was no evidence to suggest that exposure to herbicides or dioxin was associated with renal dysfunction, kidney stones, prevalence of proteinuria or albuminuria, or cells in the urine.

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APPENDIX: ABBREVIATIONS AND ACRONYMS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
ADA	American Diabetes Association
AFHS	Air Force Health Study
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
C.I.	confidence interval
CI	Cornell Index
CMI	Cornell Medical Index
CNS	central nervous system
ECG	electrocardiograph
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GADA	glutamic acid decarboxylase antibodies
GAO	Government Accounting Office
GGT	gamma glutamyltransferase
HDL	high-density lipoprotein
HLA-DR	human leukocyte antigen-DR
HRB	Halstead-Reitan Neuropsychological Test Battery
ICD-9-CM	International Classification of Diseases, 9^{th} Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10^{th} Revision, Clinical Modification
Ig	immunoglobulins
IOM	Institute of Medicine
KUB	kidney, urethra, and bladder

LDH	lactate dehydrogenase
LH	luteinizing hormone
MCMI	Millon Clinical Multiaxial Inventory
MLC	mixed lymphocyte culture
MMPI	Minnesota Multiphasic Personality Inventory
MSK	mouse stomach kidney
NIOSH	National Institute for Occupational Safety and Health
NKCA	natural killer cell assay
NKCI	natural killer cell assay with Interleukin-2
NCI	National Cancer Institute
PCT	porphyria cutanea tarda
PHA	phytohemagglutinin
ppm	parts per million
ppt	parts per trillion
PSA	prostate-specific antigen
PTSD	post-traumatic stress disorder
PWM	pokeweed mitogen
RBBB	right bundle branch block
RBC	red blood cell
RVN	Republic of Vietnam
SCL-90-R	Symptom Checklist-90-Revised
SEA	Southeast Asia
SEER	Surveillance, Epidemiology, and End Results
SHBG	sex hormone-binding globulin
SMR	standardized mortality ratio
T_3	triiodothyronine
T_4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone

USAF	United States Air Force
WAIS	Wechsler Adult Intelligence Scale
WBC	white blood cell
WMS	Wechsler Memory Scale
WRAT	Wide Range Achievement Test